=> s antibod?

L1 36482 ANTIBOD?

=> s l1 (5a) (radio?)

155108 RADIO?
L2 4504 L1 (5A) (RADIO?)

=> s l1 (5a) (radionucl?)

3946 RADIONUCL?
L3 401 L1 (5A) (RADIONUCL?)

=> s l3 (5a) (therap? or method# or administ?)

92207 THERAP?
1346823 METHOD#
121284 ADMINIST?
L4 99 L3 (5A) (THERAP? OR METHOD# OR ADMINIST?)

=> d l4 90-99 cit ab

90. 4,837,003, Jun. 6, 1989, Radiolabeled antibody fragments; Robert A. Nicolotti, 424/1.53, 156.1, 179.1; 436/512, 547, 548, 804, 813; 530/388.85, 391.5, 408, 866 [IMAGE AVAILABLE]

US PAT NO: 4,837,003 [IMAGE AVAILABLE] L4: 90 of 99

ABSTRACT:
Methods and reagents for attaching **radionuclide** metal ions to **antibody** fragments are disclosed. A coupling agent is employed which contains a maleimidyl group linked, through a divalent organic moiety, to a group capable of forming a chelate complex with the radionuclide metal ion. Antibody fragments labeled with radionuclide metal ions by the disclosed procedure are useful for in vivo diagnostic or therapeutic applications.

91. 4,831,122, May 16, 1989, Radioimmunotoxins; Donald J. Buchsbaum, et al., 530/391.3; 424/179.1; 514/885; 530/388.75, 391.1, 391.7, 808, 866 [IMAGE AVAILABLE]

US PAT NO: 4,831,122 [IMAGE AVAILABLE] L4: 91 of 99

ABSTRACT:
Radioimmunotoxins consisting of a monoclonal antibody covalently coupled to a toxin and a radionuclide. The compositions retain high binding specificity and cytotoxic activity and are useful in treating cancer and in bone marrow transplantation. The antibody component determines the selectivity. The toxin component kills the targeted cells. The radionuclide component also kills, but by a different mechanism, thus ensuring the eradication of all tumor cells. The radionuclide also allows the radioimmunotoxin to be tracked in vivo which enables the determination of its distribution throughout the body. Also, the pharmacokinetics of injected radioimmunotoxin can be determined allowing for more exact dose quantitation and administration.

92. H 545, Nov. 1, 1988, In vivo generator for radioimmunotherapy; Leonard F. Mausner, et al., 424/1.49, 178.1; 530/391.3 [IMAGE AVAILABLE]

US PAT NO: H 545 [IMAGE AVAILABLE] L4: 92 of 99

ABSTRACT:
The present invention involves labeling monoclonal antibodies with intermediate half-life radionuclides which decay to much shorter half-life daughters with desirable high energy beta emissions. Since the daughter will be in equilibrium with the parent, it can exert an in-situ tumoricidal effect over a prolonged period in a localized fashion, essentially as an "in-vivo generator". This approach circumvents the inverse relationship between half-life and beta decay energy. Compartmental modeling was used to determine the relative distribution of dose from both parent and daughter nuclei in target and non-target tissues. Actual antibody biodistribution data have been used to fit realistic rate constants for a model containing tumor, blood, and non-tumor compartments. These rate constants were then used in a variety of simulations for two generator systems, Ba-128/Cs-128 (t.sub.1/2 =2.4d/3.6m) and Pd-112/Ag-112 (t.sub.1/2 =0.9d/192m). The results show that higher tumor/background dose ratios may be achievable by virtue of the rapid excretion of a chemically different daughter during the uptake and clearance phases. This modeling also quantitatively demonstrates the favorable impact on activity distribution of a faster monoclonal antibody tumor uptake, especially when the antibody is labeled with a radionuclide with a comparable half-life.

93. 4,775,638, Oct. 4, 1988, Single vial technique for radiolabeling protein; Hidde J. Haisma, 424/1.49, 179.1; 436/547, 548, 804, 808; 530/388.2, 388.3, 388.8, 391.5, 402 [IMAGE AVAILABLE]

US PAT NO: 4,775,638 [IMAGE AVAILABLE] L4: 93 of 99

ABSTRACT:
A method for radiolabeling protein such as antibody which is performed in a single reaction vessel is described. A sealed reaction vessel having a port for addition and withdrawal of reagents preferably by syringe is used. Reagents for coupling radioisotope to the protein are added to the vessel. For radioiodination procedures, vessels can be pre-coated with the iodine coupling agent iodgen. The protein and the radioisotope are then added to the vessel and the radiolabel reaction allowed to proceed. After the reaction is complete, a resin is added to the vessel to adsorb the uncoupled radioisotope. The entire reaction mixture is then withdrawn from the vessel and the resin is separated from the protein preferably by sterile filtration.

94. 4,732,974, Mar. 22, 1988, Metal ion labeling of carrier molecules; Robert A. Nicolotti, et al., 530/391.5; 205/688; 436/512, 547, 548; 530/345, 388.85, 400; 534/10, 11, 12, 13, 14 [IMAGE AVAILABLE]

US PAT NO: 4,732,974 [IMAGE AVAILABLE] L4: 94 of 99

ABSTRACT:
A conjugate of a protein or polypeptide and a metal ion is prepared by reacting a metal ion transfer complex comprising a chelate of 4,5-dihydroxyl-m-benzenedisulfonic acid or a salt thereof with a protein or polypeptide that is covalently bound to an exogenous chelating group having a greater affinity than 4,5-dihydroxyl-m-benzenedisulfonic acid for the metal ion.

95. 4,722,892, Feb. 2, 1988, Monoclonal antibodies against metal chelates; Claude F. Meares, et al., 424/1.65, 1.53, 136.1, 155.1; 435/7.92, 188; 436/73, 81, 548, 813; 530/350, 387.3, 388.1, 391.3, 808 [IMAGE AVAILABLE]

US PAT NO: 4,722,892 [IMAGE AVAILABLE] L4: 95 of 99

ABSTRACT:
Monoclonal Antibodies which are specific for a complex of a chelating agent and a metallic ion are described. The antibody has an association constant (K.sub.a) for the complex which is at least about ten times greater than the K.sub.a for the chelating agent alone or its complex with another metal.

96. 4,659,839, Apr. 21, 1987, Coupling agents for radiolabeled antibody fragments; Robert A. Nicolotti, et al., 548/546; 436/512 [IMAGE AVAILABLE]

US PAT NO: 4,659,839 [IMAGE AVAILABLE] L4: 96 of 99

ABSTRACT:
Bifunctional coupling agent for joining radionuclide metal ions to biologically useful molecules, including antibody Fab' fragments are disclosed. The coupling agents contain a maleimide moiety and a paramagnetic or radionuclide chelating moiety. The maleimide can be used to selectively bind to free sulfhydryl groups, or amine groups.

97. 4,652,440, Mar. 24, 1987, Method of stably radiolabeling antibodies with technetium and rhenium; Chang H. Paik, et al., 424/1.49, 1.53; 530/386, 409 [IMAGE AVAILABLE]

US PAT NO: 4,652,440 [IMAGE AVAILABLE] L4: 97 of 99

ABSTRACT:
.sup.99 m Tc-labeling of antibodies and antibody fragments, either unconjugated or conjugated to DTPA, is effected in the presence of molar excess of free or carrier-bound DTPA to substantially completely inhibit direct technetium binding to non-stable binding sites on the antibody. The resultant .sup.99m Tc-labeled antibody has a stable label and is useful for, inter alia, tumor imaging by gamma scintigraphy and/or tumor therapy. Rhenium-labeling can be similarly effected.

98. 4,624,846, Nov. 25, 1986, Method for enhancing target specificity of antibody localization and clearance of non-target diagnostic and therapeutic principles; Milton D. Goldenberg, 424/1.49, 9.34; 530/387.2, 388.25, 388.3, 388.4, 388.6, 388.8, 389.3, 389.4, 389.5, 389.7, 391.3, 863, 864, 866; 600/4 [IMAGE AVAILABLE]

US PAT NO: 4,624,846 [IMAGE AVAILABLE] L4: 98 of 99

ABSTRACT:
A method for enhancing target specificity of antibody localization comprises injecting a second antibody specific to a labeled target-specific antibody to reduce the level of non-targeted circulating specific antibody, thereby increasing the localization ratio. The foregoing method is useful for imaging tumors and infectious lesions, and for therapy.

99. 4,310,505, Jan. 12, 1982, Lipid vesicles bearing carbohydrate surfaces as lymphatic directed vehicles for therapeutic and diagnostic substances; John D. Baldeschwieler, et al., 424/1.21; 264/4.1; 424/450, 493, 498; 428/402.2; 516/56, 135 [IMAGE AVAILABLE]

US PAT NO: 4,310,505 [IMAGE AVAILABLE] L4: 99 of 99

ABSTRACT:
Lipid vesicles comprising a lipid bilayer which includes analogs of cell-surface receptors such as dicetyl phosphate; stearylamine; 6-(5-cholesten-3.beta.-yloxy) hexyl 1-thio-.beta.-L-fucopyranoside; 6-(5-cholesten-3.beta.-yloxy) hexyl 1-thio-.beta.-D-galactopyranoside; 6-(5-cholesten-3.beta.-yloxy)hexyl 1-thio-.alpha.-D-mannopyranoside; 6-(5-cholesten-3-yloxy)hexyl 2-acetamido-2-deoxy-1-thio-.beta.-D-galactopyranoside; 6-(5-cholesten-3.beta.-yloxy)hexyl 6-amino-6-deoxy-1-thio-.beta.-D-galactopyranoside; or 6-(5-cholesten-3.beta.-yloxy)hexyl 6-amino-6-deoxy-1-thio-.alpha.-D-mannopyranoside; cholesterol and distearoyl phospatidylcholine, and an effective amount of physiologically compatible radioactive tracer, cytotoxic or therapeutic agent as a part of the vesicles. The vesicles of this invention can be administered to the human host and have been found to release the contents of the vesicles in a predetermined manner, i.e., controlled release, and in some cases, to be rapidly concentrated in the lymphatic system and/or liver, lungs or spleen of the host.

=> d l4 70-89 cit ab

70. 5,171,667, Dec. 15, 1992, Hybridomas producing monoclonal antibodies to mono-, di- and trifucosylated type 2 chain; Sen-itroh Hakomori, et al., 435/7.23; 424/137.1, 156.1, 178.1, 804; 435/70.21; 530/387.5, 388.1, 388.8, 388.85, 391.3, 861, 864 [IMAGE AVAILABLE]

US PAT NO: 5,171,667 [IMAGE AVAILABLE] L4: 70 of 99

ABSTRACT:
Hybridoma cell lines that produce monoclonal antibodies that differentially recognize glycolipids with mono-, di-, and trifucosylated type 2 chain structures are disclosed. The monoclonal antibodies can be used to detect specific types of tumor cells that are characterized by enrichment in mono-, di-, or trifucosylated type 2 chain structure. As such, the antibodies produced by the hybridoma cell lines are useful for diagnosis and treatment of human cancer. Also disclosed is an improved method of raising hybridoma cell lines by selecting the hybridomas by positive reactively with one or more fucosylated type 2 chain structures selected from the group consisting of III.sup.3 FucnLc.sub.4, V.sup.3 FucnLc.sub.6, III.sup.3 FucnLc.sub.6, III.sup.3 V.sup.3 Fuc.sub.2 nLc.sub.6, and III.sup.3 V.sup.3 VII.sup.3 Fuc.sub.3 nLc.sub.8.

71. 5,171,563, Dec. 15, 1992, Cleavable linkers for the reduction of non-target organ retention of immunoconjugates; Paul G. Abrams, et al., 424/1.45, 1.53, 1.69, 9.4, 94.63, 94.64, 179.1, 180.1, 181.1, 717, 720; 514/474, 562, 836, 922; 530/391.1, 391.5, 391.9, 402, 807 [IMAGE AVAILABLE]

US PAT NO: 5,171,563 [IMAGE AVAILABLE] L4: 71 of 99

ABSTRACT:
A process for reducing the non-target organ accumulation of immunoconjugates administered in vivo during therapeutic or diagnostic procedures involves the use of immunoconjugates comprising linkers that are cleavable at the non-target organs. The linkers are cleavable under conditions present, or induced, at one or more non-target organs, which include the kidneys or the liver.

72. 5,164,176, Nov. 17, 1992, Radionuclide metal chelates for the radiolabeling of proteins; Linda M. Gustavson, et al., 530/391.5; 424/1.53; 534/10, 14 [IMAGE AVAILABLE]

US PAT NO: 5,164,176 [IMAGE AVAILABLE] L4: 72 of 99

ABSTRACT:
Chelating compounds of specific structure are useful for radiolabeling targeting proteins such as antibodies. The radiolabeled antibodies, or catabolites thereof, demonstrate improved biodistribution properties, including reduced localization within the intestines.

73. 5,122,599, Jun. 16, 1992, CDNAS coding for members of the carcinoembryonic antigen family; Thomas R. Barnett, et al., 536/23.5; 435/6, 320.1; 536/23.53, 24.31 [IMAGE AVAILABLE]

US PAT NO: 5,122,599 [IMAGE AVAILABLE] L4: 73 of 99

ABSTRACT:
This invention relates to a nucleic acid comprising a base sequence which codes for a CEA family member peptide sequence or nucleic acids having a base sequence hybridizable therewith, replicable recombinant cloning vehicles having an insert comprising such nucleic acid, cells transfected, infected or injected with such cloning vehicles, polypeptides expressed by such cells, synthetic peptides derived from the coding sequence of CEA family member nucleic acids, antibody preparations specific for such polypeptides, immunoassays for detecting CEA family members using such antibody preparations and nucleic acid hybridization methods for detecting CEA family member nucleic acid sequences using a nucleic acid probe comprising the above described nucleic acid.

74. 5,120,526, Jun. 9, 1992, Method of producing metal radionuclide labeled proteins for diagnosis and therapy; Alan R. Fritzberg, et al., 530/388.15, 388.85, 389.7, 391.5, 404, 405, 866 [IMAGE AVAILABLE]

US PAT NO: 5,120,526 [IMAGE AVAILABLE] L4: 74 of 99

ABSTRACT:
Protein conjugated chelated metal radionuclides are provided for use in vivo. Intermediates are provided for preparing the polypeptide compositions efficiently.

75. 5,112,953, May 12, 1992, Radiolabeled proteins for diagnostic or therapeutic use; Linda M. Gustavson, et al., 530/391.5; 424/85.1, 94.3, 179.1; 435/188, 217; 514/8, 12, 21; 530/317, 331, 351, 391.1, 395, 408, 409; 534/10, 14; 548/517, 548; 549/491, 496; 558/254; 560/110, 251 [IMAGE AVAILABLE]

US PAT NO: 5,112,953 [IMAGE AVAILABLE] L4: 75 of 99

ABSTRACT:
Chelating compounds of specified structure are useful for radiolabeling targeting molecules such as antibodies. Cleavable linkers connect the radionuclide metal chelates to the antibodies. The radiolabeled antibodies have improved biodistribution properties, including reduced localization within the intestines and kidneys.

76. 5,110,730, May 5, 1992, Human tissue factor related DNA segments; Thomas S. Edgington, et al., 435/69.6, 252.3, 320.1; 536/23.51 [IMAGE AVAILABLE]

US PAT NO: 5,110,730 [IMAGE AVAILABLE] L4: 76 of 99

ABSTRACT:
DNA segments include DNA sequences defining a structural gene coding for a human tissue factor heavy chain protein and a precursor form of that protein are disclosed. Recombinant DNA molecules capable of expressing a human tissue factor heavy chain protein are also disclosed. Further disclosed are human tissue factor heavy chain binding site polypeptide analogs as well as methods for their use.

77. 5,084,266, Jan. 28, 1992, Method for tumor imaging utilizing a labelled tumor specific antibody and a non-tumor reactive antibody; Ian F. C. McKenzie, et al., 424/1.49, 9.34; 436/173, 547, 548, 806 [IMAGE AVAILABLE]

US PAT NO: 5,084,266 [IMAGE AVAILABLE] L4: 77 of 99

ABSTRACT:
A method for identifying and/or determining the location of a tumor which produces or is associated with a cytoplasmic, intra-cellular or cell surface marker substance, is disclosed, which comprises the steps of:
(a) injecting a human or animal subject with tumor specific antibody or a fragment thereof specific for the marker and labelled with a radioactive isotope of an element or a paramagnetic conjugate; and an irrelevant (non-tumor reactive) antibody which has been labelled with a non-radioactive isotope of the same or other element, or a non-paramagnetic conjugate; and
(b) after a period of time sufficient for selective binding of the labelled tumor specific antibody to the tumor scanning the human or animal subject with a detector to locate the site or sites of uptake of labelled antibody or fragments thereof.
Imaging compositions are also described.

78. 5,082,930, Jan. 21, 1992, Coupling agents for joining radionuclide metal ions with biologically useful proteins; Robert A. Nicolotti, et al., 424/1.53, 156.1, 179.1, 809; 435/7.1, 68.1, 272, 960, 968; 436/512, 543, 547; 514/6; 530/329, 330, 331, 391.5, 402, 404, 405, 406, 408, 866; 548/334.1, 542; 558/251; 562/575 [IMAGE AVAILABLE]

US PAT NO: 5,082,930 [IMAGE AVAILABLE] L4: 78 of 99

ABSTRACT:
This invention relates to bifunctional coupling agents useful in forming conjugates with biologically useful molecules, such as antibodies. These conjugates can be complexed with radionuclide metal ions to provide materials useful for in vivo diagnostic and therapeutic applications.

79. 5,078,673, Jan. 7, 1992, Selective removal of radiolabeled antibodies; Paul G. Abrams, 600/3, 431; 604/4 [IMAGE AVAILABLE]

US PAT NO: 5,078,673 [IMAGE AVAILABLE] L4: 79 of 99

ABSTRACT:

Methods of treating and imaging tumor sites using radiolabeled antibodies or fragments of antibodies are disclosed. Ex vivo separation of the radiolabeled antibodies is undertaken to improve image quality and treatment efficacy.

80. 5,037,630, Aug. 6, 1991, Metal radionuclide labeled proteins for diagnosis and therapy; Alan R. Fritzberg, et al., 530/386, 388.85, 391.5, 402, 866 [IMAGE AVAILABLE]

US PAT NO: 5,037,630 [IMAGE AVAILABLE] L4: 80 of 99

ABSTRACT:
Protein conjugated chelated metal radionuclides are provided for use in vivo. Intermediates are provided for preparing the polypeptide compositions efficiently.

81. 5,001,072, Mar. 19, 1991, Compositions and methods for multiple simultaneous immunoradiometric assay (IRMA) of analytes using radioisotope chelate labels; Douglas R. Olson, 436/5, 505, 538, 539, 540, 542, 545, 548, 804; 530/388.24, 391.5, 402 [IMAGE AVAILABLE]

US PAT NO: 5,001,072 [IMAGE AVAILABLE] L4: 81 of 99

ABSTRACT:
Compositions and methods are disclosed for multiple simultaneous assays of different analytes using radioactive labeled antibodies to the analytes, at least one portion of the assay being an immunoradiometric assay in which there is employed a metal isotope label, e.g., .sup.57 Co, attached to an antibody to the analyte through a chelator, e.g., ethylenediaminetetraacetic acid. Multiple simultaneous immunoradiometric assays can be performed by this method, as can multiple simultaneous assays in which one portion of the assay is an immunoradiometric assay and another portion or portions involve one or more other radioassay techniques.

82. 4,986,979, Jan. 22, 1991, Imaging tissue sites of inflammation; A. Charles Morgan, Jr., et al., 424/1.17, 1.53, 1.69, 179.1; 514/2 [IMAGE AVAILABLE]

US PAT NO: 4,986,979 [IMAGE AVAILABLE] L4: 82 of 99

ABSTRACT:
The present invention involves method of enhancing the amount of label accumulating at tissue sites of inflammation. Methods of the present invention take advantage of the up-regulation of surface antigenic markers on leukocytes upon activation thereof. A method of imaging utilizing a chemotactic peptide containing an affinity label and a radionuclide label conjugated to leukocytes is taught. Imaging applications of such enhancement are described.

83. 4,940,670, Jul. 10, 1990, Method for compounding and testing patient specific monoclonal antibodies and monoclonal antibody fragments for in vivo use; Buck A. Rhodes, 435/7.23; 424/155.1, 178.1; 436/512, 548, 813; 530/391.3 [IMAGE AVAILABLE]

US PAT NO: 4,940,670 [IMAGE AVAILABLE] L4: 83 of 99

ABSTRACT:
A kit for compounding radiolabeled monoclonal antibodies or antibody fragments for in vivo cancer diagnosis and therapy, which provides reagents for: (1) the selection of monoclonal antibodies or antibody fragments which are specific to a tumor specimen; (2) compounding the selected antibodies with a radionuclide material; and (3) quality control testing of the resulting compound. In the method of the invention, multiple aliquots of tumor biopsy material are fixed onto separate test areas of an apparatus which permits reaction with a panel of various monoclonal antibodies or antibody fragments known to react with tumor associated antigens. If one or more of the antibodies or antibody fragments bind to the tumor specimen, the reagents and antibodies or antibody fragments contained in the kit are combined with an appropriate, commercially available radionuclide. The resulting compounded radiopharmaceutical can then be administered to a patient for immunotherapy of the tumor or for cancer detection by imaging of the tumor with an imaging device to determine the extent and location of cancerous tumors. A quality control kit is used to assure that the radionuclide has been combined with the antibodies or antibody fragments to produce a formulation which will bind the radioactivity to the patient's tumor or tumor specimen.

84. 4,932,412, Jun. 12, 1990, Intraoperative and endoscopic tumor detection and therapy; Milton D. Goldenberg, 600/431, 302 [IMAGE AVAILABLE]

US PAT NO: 4,932,412 [IMAGE AVAILABLE] L4: 84 of 99

ABSTRACT:
Methods are provided for short-range intraoperative and endoscopic detection and therapy of tumors using radiolabeled antibodies and, in some cases, techniques for reducing or correcting for non-specific background radiation to improve resolution. Therapy using external radiation and/or laser or mechanical endoscopically introduced tumor removal means can be combined with the detection methods to increase precision of the tumor removal operations.

85. 4,897,255, Jan. 30, 1990, Metal radionuclide labeled proteins for diagnosis and therapy; Alan R. Fritzberg, et al., 530/391.5, 386, 388.85, 404, 405, 866 [IMAGE AVAILABLE]

US PAT NO: 4,897,255 [IMAGE AVAILABLE] L4: 85 of 99

ABSTRACT:
Protein conjugated chelated metal radionuclides are provided for use in vivo. Intermediates are provided for preparing the polypeptide compositions efficiently.

86. 4,894,326, Jan. 16, 1990, Monoclonal antibody defining oncofetal structure of fibronectin; Hidemitsu Matsuura, et al., 435/7.21, 7.23, 7.7, 7.71, 337, 344.1, 810, 948, 975; 436/518, 536, 547, 548, 813; 530/388.2, 388.25, 388.85, 391.3, 809 [IMAGE AVAILABLE]

US PAT NO: 4,894,326 [IMAGE AVAILABLE] L4: 86 of 99

ABSTRACT:
Antibody defining structure present in fibronectins from tumors and fetal tissues but absent in fibronectins from normal adult tissues and plasma; useful for diagnosing and treating human cancers.

87. 4,876,199, Oct. 24, 1989, Hybridomas producing monoclonal antibodies to mono-, di-, and trifucosylated type 2 chain; Sen-Itiroh Hakamori, 530/387.5; 424/137.1, 156.1, 804; 435/70.21, 329; 436/548; 530/861 [IMAGE AVAILABLE]

US PAT NO: 4,876,199 [IMAGE AVAILABLE] L4: 87 of 99

ABSTRACT:
Hybridoma cell lines that produce monoclonal antibodies that differentially recognize glycolipids with mono-, di-, and trifucosylated type 2 chain structures are disclosed. The monoclonal antibodies can be used to detect specific types of tumor cells that are characterized by enrichment in mono-, di-, or trifucosylated type 2 chain structure. As such, the antibodies produced by the hybridoma cell lines are useful for diagnosis and treatment of human cancer. Also disclosed is an improved method of raising hybridoma cell lines by selecting the hybridomas by positive reactivity with one or more fucosylated type 2 chain structures selected from the group consisting of III.sup.3 FucnLc.sub.4, V.sup.3 FucnLc.sub.6, III.sup.3 FucnLc.sub.6, III.sup.3 V.sup.3 Fuc.sub.2 nLc.sub.6, and III.sup.3 V.sup.3 VII.sup.3 Fuc.sub.n nLc.sub.8.

88. 4,867,962, Sep. 19, 1989, Functionally specific antibodies; Paul G. Abrams, 424/1.49, 1.53, 183.1 [IMAGE AVAILABLE]

US PAT NO: 4,867,962 [IMAGE AVAILABLE] L4: 88 of 99

ABSTRACT:
Diagnostic or therapeutic agents are attached to two or more antibody species having non-overlapping patterns of cross-reactivity to increase the relative amount of the active agent(s) delivered to desired target cells compared to non-target cells. The agents may be attached to monoclonal antibodies which bind to cancer cells so that a higher percentage of the active agent(s) localize on the target cells compared to each type of cross-reactive normal tissue.

89. 4,861,869, Aug. 29, 1989, Coupling agents for joining radionuclide metal ions with biologically useful proteins; Robert A. Nicolotti, et al., 424/1.53; 435/68.1, 272; 436/547; 514/6; 530/329, 330, 331, 345, 388.85, 391.5, 402, 404, 405, 406, 866; 930/10 [IMAGE AVAILABLE]

US PAT NO: 4,861,869 [IMAGE AVAILABLE] L4: 89 of 99

ABSTRACT:
This invention relates to bifunctional coupling agents useful in forming conjugates with biologically useful molecules, such as antibodies. These conjugates can be complexed with radionuclide metal ions to provide materials useful for in vivo diagnostic and therapeutic applications.

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*      WELCOME TO THE           *
*   U.S. PATENT TEXT FILE       *
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=> s (IL-15 or interleukin-15)

     12129 IL
   1548273 15
        44 IL-15
           (IL(W)15)
      4584 INTERLEUKIN
   1548273 15
         6 INTERLEUKIN-15
           (INTERLEUKIN(W)15)
L1       46 (IL-15 OR INTERLEUKIN-15)

=> s l1 (p) (fusion? or conjugat? or derivativ? or hybrid?)

     42354 FUSION?
     48818 CONJUGAT?
    218485 DERIVATIV?
     50094 HYBRID?
L2        5 L1 (P) (FUSION? OR CONJUGAT? OR DERIVATIV? OR HYBRID?)

=> d l2 1-5 cit ab
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1. 5,795,966, Aug. 18, 1998, Antagonists of interleukin-15; Kenneth H. Grabstein, et al., 530/388.23; 424/158.1; 435/326, 328, 335, 346, 352 [IMAGE AVAILABLE]

US PAT NO: 5,795,966 [IMAGE AVAILABLE] L2: 1 of 5

ABSTRACT:
Antagonists of mammalian interleukin-15 ("IL-15") are disclosed and include muteins of IL-15 and modified IL-15 molecules that are each capable of binding to the IL-15R.alpha.-subunit and that are incapable of transducing a signal through either the .beta.- or .gamma.-subunits of the IL-15 receptor complex. Also included are monoclonal antibodies against IL-15 that prevent IL-15 from effecting signal transduction through either the .beta.- or .gamma.-subunits of the IL-15 receptor complex. Methods of treating various disease states are disclosed, including treating allograft rejection and graft-versus-host disease.

2. 5,747,024, May 5, 1998, Vaccine adjuvant comprising interleukin-15; Kenneth H. Grabstein, et al., 424/85.2, 278.1; 514/2, 8, 12, 885; 530/351 [IMAGE AVAILABLE]

US PAT NO: 5,747,024 [IMAGE AVAILABLE] L2: 2 of 5

ABSTRACT:
Methods of enhancing a mammal's immune response to a vaccine antigen are disclosed. Interleukin-15 can be used as a vaccine adjuvant to enhance or potentiate the immune response to a vaccine. Compositions comprising an immunogenic amount of vaccine antigen and an immunogenicity-augmenting amount of IL-15 are also provided by the invention. IL-15 can be used alone in the invention or in concurrent or sequential combination with additional vaccine adjuvants.

3. 5,660,824, Aug. 26, 1997, Muscle trophic factor; Kenneth H. Grabstein, et al., 424/85.2; 530/351 [IMAGE AVAILABLE]

US PAT NO: 5,660,824 [IMAGE AVAILABLE] L2: 3 of 5

ABSTRACT:
Compositions and methods for stimulating muscle growth or differentiation in a vertebrate are disclosed. Such compositions include a muscle-trophic amount of interleukin-15 and can be used to treat a variety of conditions including disuse atrophy, wasting, various age-related disorders, secondary effects of diabetes, including glucose-intolerance, as well as muscular dystrophy, rhabdomyosarcoma and congestive heart failure. The compositions and methods of the invention find agricultural use in increasing the efficiency of meat and milk production of farm animals.

4. 5,591,630, Jan. 7, 1997, Monoclonal antibodies that bind interleukin-15 receptors; Dirk M. Anderson, et al., 435/331, 334; 530/388.22 [IMAGE AVAILABLE]

US PAT NO: 5,591,630 [IMAGE AVAILABLE] L2: 4 of 5

ABSTRACT:
There are disclosed Interleukin-15 Receptor (IL-15R) proteins, DNAs and expression vectors encoding IL-15R, and processes for producing IL-15R as products of recombinant cell cultures. Also disclosed are monoclonal antibodies that bind Interleukin-15 receptors.

5. 5,554,512, Sep. 10, 1996, Ligands for flt3 receptors; Stewart D. Lyman, et al., 435/69.5; 424/85.1; 435/69.1, 252.3, 320.1, 365; 530/351, 399; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,554,512 [IMAGE AVAILABLE] L2: 5 of 5

ABSTRACT:
Ligands for flt3 receptors capable of transducing self-renewal signals to regulate the growth, proliferation or differentiation of progenitor cells and stem cells are disclosed. The invention is directed to flt3-L as an isolated protein, the DNA encoding the flt3-L, host cells transfected with cDNAs encoding flt3-L, compositions comprising flt3-L, methods of improving gene transfer to a mammal using flt3-L, and methods of improving transplantations using flt3-L. Flt3-L finds use in treating patients with anemia, AIDS and various cancers.

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=> d his

     (FILE 'USPAT' ENTERED AT 11:48:12 ON 18 SEP 1998)
L1       46 S (IL-15 OR INTERLEUKIN-15)
L2        5 S L1 (P) (FUSION? OR CONJUGAT? OR DERIVATIV? OR HYBRID?)

=> s l1 (p) (antibod?)

     30300 ANTIBOD?
L3        7 L1 (P) (ANTIBOD?)

=> d l1 1-7 cit ab
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1. 5,807,709, Sep. 15, 1998, Secreted proteins and polynucleotides encoding them; Kenneth Jacobs, et al., 435/69.1, 252.3, 254.11, 320.1; 530/324; 536/23.1, 23.5 [IMAGE AVAILABLE]

US PAT NO: 5,807,709 [IMAGE AVAILABLE] L1: 1 of 46

ABSTRACT:
Novel polynucleotides and the proteins encoded thereby are disclosed.

2. 5,807,703, Sep. 15, 1998, Secreted proteins and polynucleotides encoding them; Kenneth Jacobs, et al., 435/69.1, 252.3, 254.11, 254.2, 320.1; 536/23.1 [IMAGE AVAILABLE]

US PAT NO: 5,807,703 [IMAGE AVAILABLE] L1: 2 of 46

ABSTRACT:
Novel polynucleotides and the proteins encoded thereby are disclosed.

3. 5,801,005, Sep. 1, 1998, Immune reactivity to HER-2/neu protein for diagnosis of malignancies in which the HER-2/neu oncogene is associated; Martin A. Cheever, et al., 435/7.24, 7.1, 7.2; 530/300, 350 [IMAGE AVAILABLE]

US PAT NO: 5,801,005 [IMAGE AVAILABLE] L1: 3 of 46

ABSTRACT:
Methods for the detection, monitoring and treatment of malignancies in which the HER-2/neu oncogene is associated are disclosed. Detection of specific T cell activation (e.g., by measuring the proliferation of T cells) in response to in vitro exposure to the HER-2/neu protein, or detection of immunocomplexes formed between the HER-2/neu protein and antibodies in body fluid, allows the diagnosis of the presence of a malignancy in which the HER-2/neu oncogene is associated. The present invention also discloses methods and compositions, including peptides, for treating such malignancies.

4. 5,795,966, Aug. 18, 1998, Antagonists of **interleukin**-**15**; Kenneth H. Grabstein, et al., 530/388.23; 424/158.1; 435/326, 328, 335, 346, 352 [IMAGE AVAILABLE]

US PAT NO: 5,795,966 [IMAGE AVAILABLE] L1: 4 of 46

ABSTRACT:
Antagonists of mammalian **interleukin**-**15** (***IL**-**15***) are disclosed and include muteins of **IL**-**15** and modified **IL**-**15** molecules that are each capable of binding to the IL-15R.alpha.-subunit and that are incapable of transducing a signal through either the .beta.- or .gamma.-subunits of the **IL**-**15** receptor complex. Also included are monoclonal antibodies against **IL**-**15** that prevent **IL**-**15** from effecting signal transduction through either the .beta.- or .gamma.-subunits of the **IL**-**15** receptor complex. Methods of treating various disease states are disclosed, including treating allograft rejection and graft-versus-host disease.

5. 5,795,909, Aug. 18, 1998, DHA-pharmaceutical agent conjugates of taxanes; Victor E. Shashoua, et al., 514/449, 549 [IMAGE AVAILABLE]

US PAT NO: 5,795,909 [IMAGE AVAILABLE] L1: 5 of 46

ABSTRACT:
The invention provides conjugates of cis-docosahexaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel

and docetaxel are preferred.

6. 5,792,850, Aug. 11, 1998, Hematopoietic cytokine receptor; James W. Baumgartner, et al., 536/23.5; 435/69.5, 335 [IMAGE AVAILABLE]

US PAT NO: 5,792,850 [IMAGE AVAILABLE] L1: 6 of 46

ABSTRACT:
Novel receptor polypeptides, polynucleotides encoding the polypeptides, and related compositions and methods are disclosed. The polypeptides comprise an extracellular ligand-binding domain of a cell-surface receptor that is expressed at high levels in lymphoid tissue, including B-cells and T-cells. The polypeptides may be used within methods for detecting ligands that stimulate the proliferation and/or development of lymphoid and myeloid cells in vitro and in vivo. Ligand-binding receptor polypeptides can also be used to block ligand activity in vitro and in vivo.

7. 5,792,628, Aug. 11, 1998, Secreted protein, BA3.1, and polynucleotides encoding same; Michael Bowman, 435/69.1, 252.3, 320.1; 530/350; 536/23.1, 23.5, 24.31 [IMAGE AVAILABLE]

US PAT NO: 5,792,628 [IMAGE AVAILABLE] L1: 7 of 46

ABSTRACT:
A novel secreted protein, BA3.1, is disclosed. Polynucleotides encoding BA3.1 are also provided.

=> d l2 kwic

US PAT NO: 5,795,966 [IMAGE AVAILABLE] L2: 1 of 5

SUMMARY:

BSUM(2)

The present invention relates generally to antagonists of a mammalian epithelium-derived T-cell factor polypeptide referred to herein as **interleukin**-**15** (***IL**-**15***). It more particularly relates to muteins of **IL**-**15**, monoclonal antibodies against **IL**-**15** and **IL**-**15** **conjugates** that each significantly reduce the ability of **IL**-**15** to stimulate the proliferation of T-lymphocytes in an in vitro CTLL assay. Also included in the invention are methods for treating various disease states in mammals where a reduction in **IL**-**15** activity is desired.

SUMMARY:

BSUM(13)

Further included in the scope of the invention are modified **IL**-**15** molecules that retain the ability to bind to the IL-15R.alpha., but have substantially diminished or no affinity for the .beta.- and/or .gamma.-subunits of the **IL**-**15** receptor complex. Modified **IL**-**15** molecules can take any form as long as the modifications are made in such a manner as to interfere with or prevent binding, usually by modification at or near the target binding site. Examples of such modified **IL**-**15** molecules include mature **IL**-**15** or a mutein of **IL**-**15** that is covalently **conjugated** to one or more chemical groups that sterically interfere with the **IL** **15**/**IL**-**15** receptor binding. For example, mature **IL**-**15** may contain site-specific glycosylation or may be covalently bound to groups such as polyethylene glycol (PEG), monomethoxyPEG (mPEG), dextran, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), poly amino acids such as poly-L-lysine or polyhistidine, albumin, gelatin at specific sites on the **IL**-**15** molecule that can interfere with binding of **IL**-**15** to the .beta.- or .gamma.-chains of the **IL**-**15** receptor complex, while maintaining the high affinity of **IL**-**15** for the IL-15R.alpha.. By taking advantage of the steric hindrance properties of the group, binding to specific receptor subunits can be antagonized. Other advantages of **conjugating** chains of PEG to proteins such as IL-2, GM-CSF, asparaginase, immunoglobulins, hemoglobin, and others are known in the art. For. . .

SUMMARY:

BSUM(28)

Recombinant production of an **IL**-**15** mutein first requires isolation of a DNA clone (i.e., cDNA) that encodes an **IL**-**15** mutein. cDNA clones are derived from primary cells or cell lines that express mammalian **IL**-**15** polypeptides. First total cell mRNA is isolated, then a cDNA library is made from the mRNA by reverse transcription. A cDNA clone may be isolated and identified using the DNA sequence information provided herein to design a cross-species **hybridization** probe or PCR primer as described above. Such cDNA clones have the sequence of nucleic acids 1-486 of SEQ ID. . .

SUMMARY:

BSUM(51)

CONJUGATED **IL**-**15** MOLECULES AND **IL**-**15** MUTEINS

SUMMARY:

BSUM(52)

The mature **IL**-**15** polypeptides disclosed herein (mature simian **IL**-**15** comprising the sequence of amino acids 49-162 of SEQ ID NO:1 and mature human **IL**-**15** having the sequence of amino acid residues 49-162 shown in SEQ ID NO:2), as well as the **IL**-**15** muteins, may be modified by forming covalent or aggregative **conjugates** with other chemical moieties. Such moieties can include PEG, mPEG, dextran, PVP, PVA, polyamino acids such as poly-L-lysine or polyhistidine, albumin and gelatin at specific sites on the **IL**-**15** molecule that can interfere with binding of **IL**-**15** to the .beta.- or .gamma.-chains of the **IL**-**15** receptor complex, while maintaining the high affinity of **IL**-**15** for the IL-15R.alpha.. Additionally, **IL**-**15** can be specifically glycosylated at sites that can interfere with binding of **IL**-**15** to the .beta.- or .gamma.-chains of the **IL**-**15** receptor complex, while maintaining the high affinity of **IL**-**15** for the IL-15R.alpha.. Preferred groups for **conjugation** are PEG, dextran and PVP. Most preferred for use in the invention is PEG, wherein the molecular weight of the. . . PEG is preferably between about 1,000 to about 20,000. A molecular weight of about 5000 is preferred for use in **conjugating** **IL**-**15**, although PEG molecules of other weights would be suitable as well. A variety of forms of PEG are suitable for. . .

SUMMARY:

BSUM(53)

The PEG moieties can be bonded to **IL**-**15** in strategic sites to take advantage of PEG's large molecular size. As described above, PEG moieties can be bonded to **IL**-**15** by utilizing lysine or cysteine residues naturally occurring in the protein or by site-specific PEGylation. One method of site specific PEGylation is through methods of protein engineering wherein cysteine or lysine residues are introduced into **IL**-**15** at specific amino acid locations. The large molecular size of the PEG chain(s) **conjugated** to **IL**-**15** is believed to block the region of **IL**-**15** that binds to the .beta.- and/or .gamma.-subunits but not the .alpha.-subunit of the **IL**-**15** receptor complex. **Conjugations** can be made by a simple addition reaction wherein PEG is added to a basic solution containing **IL**-**15**. Typically, PEGylation is carried out at either (1) about pH 9.0 and at molar ratios of SC-PEG to lysine residue. . .

SUMMARY:

BSUM(54)

Characterization of the **conjugated** PEGylated **IL**-**15** molecules can be performed by SDS-PAGE on a 4-20% gradient polyacrylamide gel, available from Novex Corp., San Diego, Calif. Conventional. . . techniques can be utilized for highly PEGylated proteins that are not visualized easily by silver staining. Purification of the PEGylated **IL**-**15** molecules can be performed using size exclusion chromatography, dialysis, ultrafiltration or affinity purification.

SUMMARY:

BSUM(57)

Alternatively, an antagonist according to the invention can take the form of a monoclonal antibody against **IL**-**15** that interferes with the binding of **IL**-**15** to any of the .alpha.-, .beta.- or .gamma.-subunits of the **IL**-**15** receptor complex. Within one aspect of the invention, **IL**-**15**, including **derivatives** thereof, as well as portions or fragments of these proteins such as **IL**-**15** peptides, can be used to prepare antibodies that specifically bind to **IL**-**15**. Within the context of the invention, the term "antibodies" should be understood to include polyclonal antibodies, monoclonal antibodies, fragments thereof. . .

SUMMARY:

BSUM(59)

Following detection of an appropriate antibody titer, positive animals are provided an additional intravenous injection of **IL**-**15** in saline. Three to four days later, the animals are sacrificed, spleen cells harvested, and spleen cells are fused to a murine myeloma cell line, e.g., NS1 or preferably P3.times.63Ag8.653 (ATCC CRL 1580). **Fusions** generate **hybridoma** cells, which are plated in multiple microtiter plates in a HAT (hypoxanthine, aminopterin and thymidine) selective medium to inhibit proliferation of non-fused myeloma cells and myeloma **hybrids**.

SUMMARY:

BSUM(60)

The **hybridoma** cells are screened by ELISA for reactivity against purified **IL**-**15** by adaptations of the techniques disclosed in Engvall et al., Immunochem. 8:871, 1971 and in U.S. Pat. No. 4,703,004. A preferred screening technique is the antibody capture technique described in Beckmann et al., (J. Immunol. 144:4212, 1990). Positive **hybridoma** cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing high concentrations of anti-**IL**-**15** monoclonal antibodies. Alternatively, **hybridoma** cells can be grown in vitro in flasks or roller bottles by various techniques. Monoclonal antibodies produced in mouse ascites. . . of antibody to protein A or protein G can also be used, as can affinity chromatography based upon binding to **IL**-**15**.

SUMMARY:

BSUM(66)

The present invention provides methods of using pharmaceutical compositions comprising an effective amount of **IL**-**15** antagonist in a suitable diluent or carrier. An **IL**-**15** antagonist of the invention can be formulated according to known methods used to prepare pharmaceutically useful compositions. An **IL**-**15** antagonist can be combined in admixture, either as the sole active material or with other known active materials, with pharmaceutically. . . formulations are described in Remington's Pharmaceutical Sciences, 16th ed. 1980, Mack Publishing Co. In addition, such compositions can contain an **IL**-**15** antagonist complexed with polyethylene glycol (PEG), metal ions, or incorporated into polymeric compounds such as polyacetic acid, polyglycolic acid, hydrogels,. . . will influence the physical state, solubility, stability, rate of in vivo release, and rate of in vivo clearance of an **IL**-**15** antagonist. An **IL**-**15** antagonist can also be **conjugated** to antibodies against tissue-specific receptors, ligands or antigens, or coupled to ligands of tissue-specific receptors.

DETDESC:

DETD(14)

Balb/c mice were injected intraperitoneally on two occasions at 3 week intervals with 10 ug of yeast-derived human **IL**-**15** in the presence of RIBI adjuvant (RIBI Corp., Hamilton, Mont.). Mouse sera was then assayed by conventional dot blot technique,. . . which animal was best to fuse. Three weeks later, mice were given an intravenous boost of 3 .mu.g of human **IL**-**15** suspended in sterile PBS. Three days later, mice were sacrificed and spleen cells were fused with Ag8.653 myeloma cells (ATCC). . . at a ratio of three spleen cells to one myeloma cell. The fusing agent was 50% PEG: 10% DMSO (Sigma). **Fusion** was plated out into twenty 96-well flat bottom plates (Corning) containing HAT supplemented DMEM media and allowed to grow for eight days. Supernatants from resultant **hybridomas** were collected and added to a 96-well plate for 60 minutes that had been first coated with goat anti-mouse Ig. Following washes, .sup.125 I-**IL**-**15** was added to each well, incubated for 60 minutes at room temperature, and washed four times. Positive wells were subsequently. . . Protein A column (Pharmacia). The clones designated as M110, M111 and M112 were each subsequently isotyped as IgG1 monoclonal antibodies. **Hybridomas** producing monoclonal antibodies M110, M111, and M112 have been deposited with the American Type Culture Collection, Rockville, Md., USA (ATCC). .

DETDESC:

DETD(20)

All **conjugation** reactions were performed with PEG, 5000 molecular weight, that was obtained in forms of succinimidyl succinate PEG (SS-PEG), succinimidyl carbonate. . . molar ratios of PEG to lysine of 1:1, 3:1, 10:1 and 100:1 (there are 9 lysine residues in each simian **IL**-**15** molecule). The reactions proceeded overnight at 4.degree. C.

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E#	FILE	FREQUENCY	TERM
E1	USPAT	3	GOLDEN, WILLIAM R/IN
E2	USPAT	1	GOLDENBAUM, PAUL E/IN
E3	USPAT	0	--> GOLDENBERG D/IN
E4	USPAT	2	GOLDENBERG, ALEC/IN
E5	USPAT	7	GOLDENBERG, ANDREW A/IN
E6	USPAT	1	GOLDENBERG, BARBARA L/IN
E7	USPAT	2	GOLDENBERG, BARRY/IN
E8	USPAT	1	GOLDENBERG, BORIS/IN
E9	USPAT	2	GOLDENBERG, CAROL/IN
E10	USPAT	2	GOLDENBERG, CHARLES/IN
E11	USPAT	2	GOLDENBERG, DANIEL/IN
E12	USPAT	1	GOLDENBERG, DAVID A/IN

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E13	USPAT	11	GOLDENBERG, DAVID M/IN
E14	USPAT	2	GOLDENBERG, DAVID MILTON/IN
E15	USPAT	2	GOLDENBERG, DAVID Z/IN
E16	USPAT	3	GOLDENBERG, EMANUEL/IN
E17	USPAT	8	GOLDENBERG, EMMANUEL/IN
E18	USPAT	1	GOLDENBERG, ENRIQUE A/IN
E19	USPAT	2	GOLDENBERG, EPHRAIM/IN
E20	USPAT	2	GOLDENBERG, FRANK G/IN
E21	USPAT	1	GOLDENBERG, HAROLD JACOB/IN
E22	USPAT	1	GOLDENBERG, HARRY/IN
E23	USPAT	2	GOLDENBERG, HENRY R/IN
E24	USPAT	1	GOLDENBERG, HENRY ROBERT/IN

=> s e13-14

11 "GOLDENBERG, DAVID M"/IN
2 "GOLDENBERG, DAVID MILTON"/IN
L4 13 ("GOLDENBERG, DAVID M"/IN OR "GOLDENBERG, DAVID MILTON"/IN)

=> d l4 1-13 cit ab

1. 5,736,119, Apr. 7, 1998, Detection and therapy of lesions with biotin/avidin-metal chelating protein conjugates; **David Milton** **Goldenberg**, et al., 424/1.53, 9.3, 9.34, 178.1; 530/367, 391.3, 391.5, 400, 402; 548/303.7 [IMAGE AVAILABLE]

US PAT NO: 5,736,119 [IMAGE AVAILABLE] L4: 1 of 13

ABSTRACT:
Improved methods of detecting and/or treating lesions in a patient are provided. The improved methods comprise the steps of (a) parenterally injecting a subject with a targeting composition comprised of a conjugate of biotin and targeting protein or of an avidin and targeting protein, wherein the targeting protein preferentially binds to a marker substance produced or associated with the targeted lesion, and allowing the targeting protein conjugate to preferentially accrete at the targeted lesion; (b) then parenterally injecting a clearing composition comprised of (i) avidin, when the targeting composition is a biotin-targeting protein conjugate, or (ii) biotin, when the targeting composition is a avidin-targeting protein conjugate, and allowing the clearing composition to substantially clear the targeting composition from non-targeted sites and to bind to the targeting composition accreted at the targeted lesion; (c) parenterally injecting a localization agent which may be the same or different form the clearing agent; (d) parenterally injecting a detection or therapeutic composition comprised of a conjugate of (i) avidin and naturally occurring metal-ion chelating protein chelated with chelatable metal detection or therapeutic agent when the clearing composition is biotin, or (ii) biotin and naturally occurring metal-ion carry protein chelated with chelatable a metal detection or therapeutic agent when the clearing agent is avidin, and allowing the composition to accrete at the targeted lesion. The improvement is that the use of the chelating protein to chelate a chelatable metal therapeutic or detection agent amplifies the amount of detection or therapeutic agent at the targeted site.

2. 5,716,595, Feb. 10, 1998, Intraperative, intravascular and endoscopic tumor and lesion detection and therapy with monovalent antibody fragments; **David M. Goldenberg**, 424/1.49, 1.11, 178.1, 181.1 [IMAGE AVAILABLE]

US PAT NO: 5,716,595 [IMAGE AVAILABLE] L4: 2 of 13

ABSTRACT:
Methods are provided for close-range intraoperative, endoscopic and intravascular detection and treatment of lesions, including tumors and non-malignant lesions. The methods use agents labeled with isotopic and non-isotopic agents. Also provided are methods for detection and treatment of lesions with photodynamic agents and methods of treating lesions with a protein conjugated to an agent capable of being activated to emit Anger electron or other ionizing radiation. Compositions and kits useful in the above methods are also provided.

3. 5,698,405, Dec. 16, 1997, Method of reducing immunogenicity; **David** **M. Goldenberg**, 435/7.5; 424/9.34; 530/367, 402 [IMAGE AVAILABLE]

US PAT NO: 5,698,405 [IMAGE AVAILABLE] L4: 3 of 13

ABSTRACT:
The immunogenicity of avidin, a therapeutic agent moiety of a conjugate, or a targeting composition is reduced by coupling the immunogenic agent with a carbohydrate polymer or polyol groups, such as polysaccharides (e.g. dextran), polyethylene glycol and the like.

4. 5,698,178, Dec. 16, 1997, Polyspecific immunoconjugates and antibody

composites for targeting the multidrug resistant phenotype; **David M.** **Goldenberg**, 424/1.49, 1.53, 9.341, 9.6 [IMAGE AVAILABLE]

US PAT NO: 5,698,178 [IMAGE AVAILABLE] L4: 4 of 13

ABSTRACT:
Polyspecific immunoconjugates and antibody composites that bind a multidrug transporter protein and an antigen associated with a tumor or infectious agent are used to overcome the multidrug resistant phenotype. These immunoconjugates and composites also can be used diagnostically to determine whether the failure of traditional chemotherapy is due to the presence of multidrug resistant tumor cells, multidrug resistant HIV-infected cells or multidrug resistant infectious agents.

5. 5,686,578, Nov. 11, 1997, Polyspecific immunoconjugates and antibody composites for targeting the multidrug resistant phenotype; **David M.** **Goldenberg**, 530/387.3, 388.2, 388.4, 388.8, 388.85, 389.1, 389.5, 389.7, 391.1, 391.9 [IMAGE AVAILABLE]

US PAT NO: 5,686,578 [IMAGE AVAILABLE] L4: 5 of 13

ABSTRACT:
Polyspecific immunoconjugates and antibody composites that bind a multidrug transporter protein and an antigen associated with a tumor or infectious agent are used to overcome the multidrug resistant phenotype. These immunoconjugates and composites also can be used diagnostically to determine whether the failure of traditional chemotherapy is due to the presence of multidrug resistant tumor cells, multidrug resistant HIV-infected cells or multidrug resistant infectious agents.

6. 5,677,427, Oct. 14, 1997, Chimeric antibody for detection and therapy of infectious and inflammatory lesions; **David M. Goldenberg**, et al., 530/387.3; 424/9.1, 133.1; 435/69.6, 252.33; 530/388.7, 391.3 [IMAGE AVAILABLE]

US PAT NO: 5,677,427 [IMAGE AVAILABLE] L4: 6 of 13

ABSTRACT:
A chimeric antibody-agent conjugate for targeting foci of leukocyte accretion comprises a recombinant chimera having an antigen-binding hypervariable region which binds specifically to granulocytes, and a constant region of a human immunoglobulin having an Fc portion with high affinity for receptors on human mononuclear lymphoid cells, said chimera being conjugated to at least one diagnostic agent or therapeutic agent. A method for targeting an imaging or therapy agent to an inflammatory or infectious lesion comprises injecting a mammal parenterally with an effective amount for targeting of the above chimeric anti-leukocyte conjugate.

7. 5,637,288, Jun. 10, 1997, Chimeric antibody for detection and therapy of infectious and inflammatory lesions; **David M. Goldenberg**, et al., 424/1.49, 1.11, 9.3, 153.1, 178.1, 182.1 [IMAGE AVAILABLE]

US PAT NO: 5,637,288 [IMAGE AVAILABLE] L4: 7 of 13

ABSTRACT:
A chimeric antibody-agent conjugate for targeting foci of leukocyte accretion comprises a recombinant chimera having an antigen-binding hypervariable region which binds specifically to granulocytes, and a constant region of a human immunoglobulin having an Fc portion with high affinity for receptors on human mononuclear lymphoid cells, said chimera being conjugated to at least one diagnostic agent or therapeutic agent. A method for targeting an imaging or therapy agent to an inflammatory or infectious lesion comprises injecting a mammal parenterally with an effective amount for targeting of the above chimeric anti-leukocyte conjugate.

8. 5,632,968, May 27, 1997, Detection of cardiovascular lesions; **David** **M. Goldenberg**, 424/1.49, 9.34 [IMAGE AVAILABLE]

US PAT NO: 5,632,968 [IMAGE AVAILABLE] L4: 8 of 13

ABSTRACT:
This invention relates to reagents and methods for detecting and imaging cardiovascular lesions such as atherosclerotic plaques, vascular clots including thrombi and emboli, myocardial infarction, and other organ infarcts. Monospecific antibody imaging agent conjugates specific for one type of leukocyte, as well as multispecific antibody imaging agent conjugates specific for at least one type of leukocyte and for antigens associated with fibrin, myosin or platelets, are used in the present invention. Multispecific antibody imaging agent conjugates specific for at least two different antigens selected from the group consisting of fibrin-, myosin- and platelet associated antigens are also provided.

9. 5,601,825, Feb. 11, 1997, Therapeutic conjugates of toxins and drugs; Hans J. Hansen, et al., 424/183.1, 178.1; 530/391.7, 391.9 [IMAGE AVAILABLE]

US PAT NO: 5,601,825 [IMAGE AVAILABLE] L4: 9 of 13

ABSTRACT:
Provided are conjugates useful in cancer or infectious disease therapy. The conjugate is a drug or modified toxin which is a native toxin devoid of a functioning receptor binding domain and a protein which reacts with a substance associated with a targeted cell or pathogen. The targeted substance internalizes the conjugate into the cell cytoplasm, and the kills the cell. The protein prior to conjugation has at least one mercapto group which becomes a site for conjugation to the toxin or drug. Also provided are methods of therapy, methods for producing the conjugate and pharmaceuticals compositions of the conjugates.

10. 5,541,297, Jul. 30, 1996, Therapeutic conjugates of toxins and drugs; Hans J. Hansen, et al., 530/391.7; 424/178.1, 183.1; 530/391.1 [IMAGE AVAILABLE]

US PAT NO: 5,541,297 [IMAGE AVAILABLE] L4: 10 of 13

ABSTRACT:
Provided are conjugates useful in cancer or infectious disease therapy. The conjugate is a drug or modified toxin which is a native toxin devoid of a functioning receptor binding domain and a protein which reacts with a substance associated with a targeted cell or pathogen. The targeted substance internalizes the conjugate into the cell cytoplasm, and the kills the cell. The protein prior to conjugation has at least one mercapto group which becomes a site for conjugation to the toxin or drug. Also provided are methods of therapy, methods for producing the conjugate and pharmaceuticals compositions of the conjugates.

11. 5,525,338, Jun. 11, 1996, Detection and therapy of lesions with biotin/avidin conjugates; **David M. Goldenberg**, 424/178.1, 1.41, 1.49, 85.1, 94.3, 183.1, 193.1; 514/21 [IMAGE AVAILABLE]

US PAT NO: 5,525,338 [IMAGE AVAILABLE] L4: 11 of 13

ABSTRACT:
Methods are provided for detecting and/or treating lesions in a patient. The methods use a targeting composition comprised of a biotin and targeting protein conjugate or an avidin and targeting protein conjugate; optionally, a clearing composition comprised of avidin, when the targeting composition is a biotin conjugate, or biotin, when the targeting composition is a avidin conjugate; a detection or therapeutic composition comprised of a conjugate of avidin or biotin with a targeting protein and detection or therapeutic agent; and, optionally, another detection or therapeutic composition comprised of avidin or biotin conjugated to a detection or therapeutic agent. Compositions and kits useful in the methods are also provided.

12. 5,364,612, Nov. 15, 1994, Detection of cardiovascular lesions; **David M. Goldenberg**, 424/1.53, 1.49, 9.341, 136.1, 152.1, 153.1, 154.1, 172.1, 173.1; 530/391.3 [IMAGE AVAILABLE]

US PAT NO: 5,364,612 [IMAGE AVAILABLE] L4: 12 of 13

ABSTRACT:
This invention relates to reagents and methods for detecting and imaging cardiovascular lesions such as atherosclerotic plaques, vascular clots including thrombi and emboli, myocardial infarction, and other organ infarcts. Monospecific antibody imaging agent conjugates specific for one type of leukocyte, as well as multispecific antibody imaging agent conjugates specific for at least one type of leukocyte and for antigens associated with fibrin, myosin or platelets, are used in the present invention. Multispecific antibody imaging agent conjugates specific for at least two different antigens selected from the group consisting of fibrin-, myosin- and platelet associated antigens are also provided.

13. 3,865,689, Feb. 11, 1975, Method of producing carcinoembryonic antigens; **David Milton Goldenberg**, 435/70.3, 259 [IMAGE AVAILABLE]

US PAT NO: 3,865,689 [IMAGE AVAILABLE] L4: 13 of 13

ABSTRACT:
A method of cultivating carcinoembryonic antigen producing cells in vitro in a highly supplemented growth medium is disclosed.

FAOM Checklist

Appl. Ser. No. .. 08/949,758 FD 10/14/97

date EFD 10/17/96 .. via ...60/028,430...

Briefed yes

Form 948 present? none

Declaration (06-05)
PCT referred to? N/A
priority dates OK? yes
continuing dates OK? yes
CIP duty? (06-05-09) N/A

Meets conditions for priority (02-09) yes

Sequences in compliance? N/A

Restriction/Election? yes

Priority Docs present? N/A

File wrapper labeled OK and initialed? yes

Title (06-11) OK

Abstract (06-12 missing) OK
(06-13 informs)
(06-14,15 content)

Figures (06-22) none

Brief Description none

Amendments? none

IDS checked yes

Seq Srch requested N/A

Copies of refs requested yes

07-29, 06-31?

07-34

=> s (RNAse#)

L5 4712 (RNASE#)

=> s l5 (5a) (cytokine#)

5552 CYTOKINE#
L6 0 L5 (5A) (CYTOKINE#)

=> s l5 (5a) (interleukin#)

6891 INTERLEUKIN#
L7 0 L5 (5A) (INTERLEUKIN#)

=> s (onconase#)

L8 5 (ONCONASE#)

=> s l8 (p) (cytokine#)

5552 CYTOKINE#
L9 0 L8 (P) (CYTOKINE#)

=> s l5 (p) (cytokine#)

5552 CYTOKINE#
L10 28 L5 (P) (CYTOKINE#)

=> d l10 1-28 kwic

US PAT NO: 5,922,546 [IMAGE AVAILABLE] L10: 1 of 28

SUMMARY:

BSUM(53)

In addition, inflammation, neural degeneration, allergic disorders, or other disorders involving a dis-regulation of the substrate **cytokines** or receptors, can be diagnosed by methods comprising determining from a sample derived from a subject an abnormally decreased or. . . any of the methods well known in the art for the quantitation of polynucleotides, such as, for example, PCR, RT-PCR, **RNase** protection, Northern blotting and other hybridization methods. Assay techniques that can be used to determine levels of a protein, such. . .

US PAT NO: 5,905,089 [IMAGE AVAILABLE] L10: 2 of 28

DETDESC:

DETD(22)

The . . . of treatment may be monitored by detection methods used in the art, including immunoassays, Northern and Western blot analysis, and **RNase** protection assays. Examples of immunoassays that may be used to detect and monitor levels of **cytokines**, chemokines, mitogens, or other proteins affected by an active sesquiterpene lactone in a sample include competitive and non-competitive immunoassays, in. . .

DETDESC:

DETD(28)

One . . . on transcription of the kinase or stability of the mRNA may be measured, for example, by Northern blot analysis or **RNase** protection assay (see for example, Current Protocols in Molecular Biology, Ausubel, et al., Wiley Interscience, 1994, incorporated herein by reference). The level of **cytokine**, chemokine, mitogen, or other protein inhibited by an active sesquiterpene lactone may also be monitored by these and other standard. . .

US PAT NO: 5,871,726 [IMAGE AVAILABLE] L10: 3 of 28

DETDESC:

DETD(25)

Genetic . . . e.g. the a chains of diphtheria, ricin, abrin, etc., genes that encode an engineered cytoplasmic variant of a nuclease (e.g. **RNase** A) or protease (e.g. trypsin, papain, proteinase K, carboxypeptidase, etc.), or encode the Fas gene, and the like. Other genes of interest include **cytokines**, antigens, transmembrane proteins, and the like, such as IL-1, -2, -6, -12, GM-CSF, G-CSF, M-CSF, IFN-.alpha., -.beta., -.gamma., TNF-.alpha., -.beta.,. . .

US PAT NO: 5,871,723 [IMAGE AVAILABLE] L10: 4 of 28

DETDESC:

DETD(223)

Specificity of the hybridization is determined by: a) pretreating some of the slides with **RNase** A (40 ug/ml in 2XSSC) prior to the hybridization with specific **cytokine** anti-sense probe; b) pretreating with excess cold anti-sense probe; and/or c) using a labeled sense probe. A computer enhanced video. . .

US PAT NO: 5,866,787 [IMAGE AVAILABLE] L10: 5 of 28

SUMMARY:

BSUM(12)

The interferon family of **cytokines** are believed to induce an antiviral state in cells of higher vertebrates. J. Vilcek, G. C. Sen, In Virology, B.. . . G. et al.: Nature, 268:537 (1977), and Marie, I. et al.: J. Biol. Chem., 267:9933 (1992); and 2) the 2-5A-dependent **Rnase** L. Clemens, M. J. et al.: Cell, 13:565 (1978), Slattery et al.: Proc. Natl. Acad. Sci. USA, 76:4778 (1978), and Zhou, A. et al.: Cell, 72:753 (1993). 2-5A is thought to activate **Rnase** L which cleaves viral and cellular single-stranded RNAs, predominantly after UpNp sequences. Floyd-Smith, G. E. et al.: Science, 212:1020 (1981);. . . e.g., Gribaudo G. et al.: J. Virol., 65:1748 (1991), for instance as replicative intermediates of RNA viruses, RNA degradation by **Rnase** L is believed to frequently occur in interferon-treated, virus-infected cells. See Wreschner, D. H. et al.: Nucleic Acids Res., 9:1571. . .

DETDESC:

DETD(93)

In this Example III, neither 2-5A synthetase activity (Table V) nor **RNase** Lactivity, as measured either by 2-5A binding, see FIG. 29, or by 2-5A-dependent ribonuclease activities, see FIG. 30, is detectable. . . See, Devash, Y. et al.: J. Biol Chem, 259:3482-3486 (1984). Southern and northern blotsprobed with human 2-5A synthetase cDNA or **RNase** L cDNA are also negative. See FIGS. 27 and 28. These results appear to support the report of Cayley,P. J.. . . Biochem Biophys Res Commun, 108:1243-1250 (1982), which showsan absence of 2-5A synthetase activity or 2-5A binding activity (a measure of **RNase** L) in Nicotiana glutinosa and Nicotiana tabacum cv. xanthi-nc. Inaddition, no 2-5A synthetase is detected and no 2-5A is detected. . . et al.: J. Biol Chem, 259:3482-3486 (1984); and Devach, Y. et al.: Meth Enz, 119:759-761 (1986)) or to induce of **cytokine** activities and stress proteins in plants (Kulaeva, O. N. et al.: Plant Mol Biol, 20:383-393 (1992).

US PAT NO: 5,861,290 [IMAGE AVAILABLE] L10: 6 of 28

DETDESC:

DETD(10)

The . . . as antisense mRNA, and ribozymes (V. Walbot et al, Nature (1988) 334:196-97). Another class of effector genes includes genes encoding **cytokines** useful for antiviral or anti-hyperproliferative disorders, such as tumor necrosis factor, .alpha. interferon, .beta. interferon, gamma interferon, transforming growth factor-.beta.,. . . invention include protease inhibitors, which may inhibit essential protein processing, and inhibitors of glycosylation, phosphorylation, or myristylation of viral proteins. **RNase** is also suitable. One may alternatively "titrate" the trans-acting factor by providing a plurality of cis-acting sequences in conjunction with. . .

CLAIMS:

CLMS(2)

2. . . .
said host cell when said hyperproliferative disorder arises, said effector gene product being selected from the group consisting of a **cytokine**, a ribozyme, a glycosylation inhibitor, a myristylation inhibitor and an **RNase**.

CLAIMS:

CLMS(12)

12. . . .
cell when said hyperproliferative disorder or said infection arises, said gene product being selected from the group consisting of a **cytokine**, a ribozyme, a glycosylation inhibitor, a myristylation inhibitor, and an **RNase**.

CLAIMS:

CLMS(28)

28. . . .
said host cell is infected by said infectious agent, said effector gene

product being selected from group consisting of a **cytokine**, a ribozyme, a glycosylation inhibitor, a myristylation inhibitor and an **RNase**.

CLAIMS:

CLMS(37)

37. . . .
host cell is infected by said infectious agent, said gene product further being selected from the group consisting of a **cytokine**, a glycosylation inhibitor, a myristylation inhibitor, and an **RNase**.

CLAIMS.

CLMS(62)

62. . . .
host cell is infected by said infectious agent, said gene product further being selected from the group consisting of a **cytokine**, a ribozyme, a glycosylation inhibitor, a myristylation inhibitor, and an **RNase**.

US PAT NO: 5,846,822 [IMAGE AVAILABLE] L10: 7 of 28

DETDESC:

DETD(14)

The . response in a cell. For example, an agent can be a small organic molecule, a biological response modifier (e.g., a **cytokine**) or a molecule which can crosslink surface structures on the cell (e.g., an antibody). Expression of pp32 mRNA in a. . . pp32 cDNA, e.g., SEQ ID NO: 1). Alternatively, pp32 mRNA can be detected by standard hybridization techniques (e.g., Northern hybridization; **RNase** protection) using probes encompassing all or part of a nucleotide sequence encoding a pp32 protein (e.g., all or part of. . .

US PAT NO: 5,843,642 [IMAGE AVAILABLE] L10: 8 of 28

DETDESC:

DETD(75)

Abnormal . agarose gels (61-64). This technique has been employed in samples of as few as 100 cells to identify mRNAs for **cytokine** expression (62). We are using this mRNA phenotyping approach in the analysis of retinoid receptor genes that are unexpressed at the level of total cellular or the more sensitive level possible within poly A+ or **RNAse** protected RNA. Isolated cells from the patient are homogenized in 4M guanidine thiocyanate containing carrier RNA or glycogen. Aliquots are. . .

US PAT NO: 5,843,440 [IMAGE AVAILABLE] L10: 9 of 28

SUMMARY:

BSUM(14)

Host . . . II, and non-classical class I HLA (E, F and G) for modulating immunoregulation, soluble T or B cell surface proteins, **cytokines**, interleukins and growth factors such as IL 1, 2, 3, 4, 6, 10, soluble IL2 receptor, M-CSF, G-CSF, GM-CSF, platelet. . . complement factors, PAF aceter, ions such as calcium, potassium, magnesium, aluminum, iron, etc, enzymes such as proteases, kinases, phosphatases, DNAses, **RNAses**, lipases and other enzymes affecting cholesterol and other lipid metabolism, esterases, dehydrogenases, oxidases, hydrolases, sulphatases, cyclases, transferases, transaminases, atriopeptidases, carboxylases. . .

US PAT NO: 5,840,840 [IMAGE AVAILABLE] L10: 10 of 28

DETDESC:

DETD(13)

Possible . . . moiety and ending with the recognition moiety. Mammalian cells have been used to express and secrete hybrid molecules such as antibody-**cytokines** (Hoogenboom, H., Raus, J. & Volckaert, 1991, Biochem Biophys Acta 1096:345-354; G., Hoogenboom, H., Volckaert, G. & Raus, Jr., 1991,. . . (Casadei et al., 1990, Proc. Natl. Acad. Sci. USA 87:2047-2051; Williams et al., 1986, Gene 43:319-324).) Recombinant humanized chimeric antibody-human **RNase** fusion proteins are preferred cytotoxic reagents as the immunogenicity of the reagent in humans is reduced.

US PAT NO: 5,837,542 [IMAGE AVAILABLE] L10: 11 of 28

DETDESC.

DETD(18)

The . . . will be delivered by incorporation into liposomes, by complexing with cationic lipids, by microinjection, or by expression from DNA vectors. **Cytokine**-induced ICAM-1 expression will be monitored by ELISA, by indirect immunofluoresence, and/or by FACS analysis. ICAM-1 mRNA levels will be assessed by Northern, by **RNAse** protection, by primer extension or by quantitative RT-PCR analysis. Ribozymes that block the induction of ICAM-1 protein and mRNA by. . .

US PAT NO: 5,837,510 [IMAGE AVAILABLE] L10: 12 of 28

DETDESC:

DETD(10)

The . . . as antisense mRNA, and ribozymes (V. Walbot et al, Nature (1988) 334:196-97). Another class of effector genes includes genes encoding **cytokines** useful for antiviral or anti-hyperproliferative disorders, such as tumor necrosis factor, .alpha. interferon, .beta. interferon, gamma interferon, transforming growth factor-.beta.,. . . invention include protease inhibitors, which may inhibit essential protein processing, and inhibitors of glycosylation phosphorylation, or myristylation of viral proteins. **RNase** is also suitable. Another effector gene may encode an antibody specific for an antigen associated with the infection or hyperproliferative. . .

CLAIMS:

CLMS(1)

What . . .
susceptible to destruction when said hyperproliferative disorder arises, said effector gene product being selected from the group consisting of a **cytokine**, a ribozyme, a glycosylation inhibitor, a myristylation inhibitor, and an **RNase**.

CLAIMS:

CLMS(13)

13. . . .
susceptible to destruction when said hyperproliferative disorder arises, said effector gene product being selected from the group consisting of a **cytokine**, a ribozyme, a protease inhibitor, a glycosylation inhibitor, a myristylation inhibitor, an **RNase**, and an antisense RNA.

CLAIMS:

CLMS(22)

22. . . .
host cell is infected by said infectious agent, said effector gene product being selected from the group consisting of a **cytokine**, a ribozyme, a glycosylation inhibitor, a myristylation inhibitor, and an **RNase**.

US PAT NO: 5,776,690 [IMAGE AVAILABLE] L10: 13 of 28

SUMMARY:

BSUM(5)

Many . . . Clin. Exp. Immunol., 83:441-446, 1991; Barker et al., Clin. Infect. Dis., 18:S136-S141,1994). The interferons area family of antiviral and antiproliferative **cytokines** which exert their pleiotropic effects through the induction of several antiviral genes (Lengyel, Proc. Nati. Acad. Sci. USA, 90:5893-5895,1993; Pestka. . . Biochem. Biophys. Res. Commun., 100:847-856, 1981; Mordechai et al., Virology, 206:913-922, 1995). Subnanomolar concentrations of 2-5A activate a latent endonuclease, **RNase** L, which is the terminal enzyme in the 2-5A system (Zhou et al., Cell, 72:753-765, 1993). Activated **RNase** L degrades mRNA and rRNA on the 3' side of a UpNp sequence, resulting in inhibition of viral and cellular. . .

US PAT NO: 5,766,859 [IMAGE AVAILABLE] L10: 14 of 28

SUMMARY:

BSUM(5)

Many . . . Immunol., 83:441-446, 1991; Barker et al., Clin. Infect. Dis., 18:S136-S141, 1994). The interferons are a family of antiviral and antiproliferative **cytokines** which exert their pleiotropic effects through the induction of several antiviral genes (Lengyel, Proc. Natl. Acad. Sci. USA, 90:5893-5895, 1993;. . . Biochem. Biophys. Res. Commun., 100:847-856, 1981; Mordechai et al., Virology, 206:913-922, 1995). Subnanomolar concentrations of 2-5A activate a latent endonuclease, **RNase** L, which is the terminal enzyme in the 2-5A

system (Zhou et al., Cell, 72:753-765, 1993). Activated **RNase** L degrades mRNA and rRNA on the 3' side of a UpNp sequence, resulting in inhibition of viral and cellular. . .

US PAT NO: 5,731,343 [IMAGE AVAILABLE] L10: 15 of 28

DETDESC:

DETD(28)

The . . . can be monitored by common detection methods used in the art, such as immunoassays, Northern and Western blot analysis and **RNase** protection assays. Examples of types of immunoassays which can be utilized to detect and monitor levels of **cytokines**, chemokines, mitogens, or other proteins affected by radicicol in a sample, include competitive and non-competitive immunoassays in either a direct. . .

DETDESC:

DETD(34)

In . . . on transcription of the kinase or stability of the mRNA can be measured, for example, by Northern blot analysis or **RNase** protection assay (see for example, Current Protocols in Molecular Biology, Ausubel, et al., Wiley Interscience, 1994, incorporated herein by reference). The level of **cytokine**, chemokine, mitogen or other radicicol inhibited protein described herein can also be monitored by these and other standard molecular biology. . .

DETDESC:

DETD(121)

In . . . suggest that the inhibition of COX-2 expression by radicicol occurs mainly at post-transcriptional steps. In addition, the results of the **RNase** protection assays indicate that radicicol also inhibits the expression of several pro-inflammatory **cytokines**, including IL-1 and TNF-.alpha..

US PAT NO: 5,710,134 [IMAGE AVAILABLE] L10: 16 of 28

SUMMARY:

BSUM(22)

The . . . be used for the preparation of fusion proteins in combination with procoagulating factors (Denekamp, Cancer Topics 6, 6-8, 1986) or **cytokines** or chemokines (Mulligan, Science 260, 926-932, 1993). Associated with vector DNA, which codes for proinflammatory, immunoregulatory or proliferation-inhibiting proteins, the. . . origin (ricin A, diphtheria toxin A, Pseudomonas exotoxin A; Burrows and Thorpe, PNAS 90, 8996-9000, 1993) or human origin (angiogenin, **RNAses**; Rybak et al., PNAS 89, 3165-3169, 1992). Furthermore, linkage with toxic synthetics or natural substances, such as e.g. alkylating agents,. . .

US PAT NO: 5,707,624 [IMAGE AVAILABLE] L10: 17 of 28

DETDESC:

DETD(67)

In . . . are washed twice for 10 min in 2.times.SSC followed by treatment for 30 min at 22.degree. C. with 20 .mu.g/ml **RNase** A, washing 2.times. for 10 min in 2.times.SSC, for 2 hr in 0.2.times.SSC at 42.degree. C. and finally 2.times. for. . . stained with hematoxylin and eosin. Contiguous sections are used for immunohistochemistry and immunoperoxidase stained with polyclonal antibodies to the various **cytokines** and adhesion molecules. Briefly, slides are incubated with primary antibodies which have been biotinylated, followed by incubation with Vectastain ABC. . .

US PAT NO: 5,698,443 [IMAGE AVAILABLE] L10: 18 of 28

SUMMARY:

BSUM(36)

Genetic . . . e.g. the .alpha. chains of diphtheria, ricin, abrin, etc., genes that encode an engineered cytoplasmic variant of a nuclease (e.g. **RNase** A) or protease (e.g. trypsin, papain, proteinase K, carboxypeptidase, etc.), or encode the Fas gene, and the like. Other genes of interest include **cytokines**, antigens, transmembrane proteins, and the like, such as IL-1, -2, -6, -12, GM-CSF, G-CSF, M-CSF, IFN.alpha., -.beta., -.gamma., TNF.alpha., -.beta.,. . .

US PAT NO: 5,688,915 [IMAGE AVAILABLE] L10: 19 of 28

DETDESC:

DETD(28)

Various . . . agent or mode of operation, the present invention contemplates testing of a number of agents, including, but not limited to, **cytokines**, non-steroidal anti-inflammatory agents, steroids, antiviral compounds (nucleotide analog-type inhibitors of the reverse transcriptase, such as but not limited to AZT. . . into cells, such as soluble CD4 protein (sCD4), and chimeric sCD4 derivatives, such as CD4-IgG and CD4-PE40; blockers of HIV **RNaseH** activity, such as the AZT derivative azidothymidine monophosphate; drugs that alter the intracellular milieu to create conditions less favorable for. . .

US PAT NO: 5,674,680 [IMAGE AVAILABLE] L10: 20 of 28

DETDESC:

DETD(21)

Other . . . into cells, such as soluble CD4 protein (sCD4), and chimeric sCD4 derivatives, such as CD4-IgG and CD4-PE40; blockers of HIV **RNaseH** activity, such as the AZT derivative azidothymidine monophosphate; drugs that alter the intracellular milieu to create conditions less favorable for. . . thalidomine (which seems to lower blood TNF-.alpha. levels; and manipulation of the immune system and viral replication with naturally occurring **cytokines** and lymphokines, or other agonists or antogonists of these systems. Accordingly, the present invention provides an accurate and effective prognostic. . .

US PAT NO: 5,658,780 [IMAGE AVAILABLE] L10: 21 of 28

DETDESC:

DETD(26)

The ribozymes will be tested for function in vivo by analyzing **cytokine**-induced VCAM-1, ICAM-1, IL-6 and IL-8 expression levels. Ribozymes will be delivered to cells by incorporation into liposomes, by complexing with cationic lipids, by microinjection, or by expression from DNA vectors. **Cytokine**-induced VCAM-1, ICAM-1, IL-6 and IL-8 expression will be monitored by ELISA, by indirect immunofluoresence, and/or by FACS analysis. Rel A mRNA levels will be assessed by Northern analysis, **RNAse** protection or primer extension analysis or quantitative RT-PCR. Activity of NF-.kappa.B will be monitored by gel-retardation assays. Ribozymes that block. . .

US PAT NO: 5,627,025 [IMAGE AVAILABLE] L10: 22 of 28

DETDESC:

DETD(40)

Although . . . agent or mode of operation, the present invention contemplates testing of a number of agents, including, but not limited to, **cytokines**, non-steroidal anti-inflammatory agents, steroids, antiviral compounds (nucleotide analog-type inhibitors of the reverse transcriptase, such as but not limited to AZT. . . into cells, such as soluble CD4 protein (sCD4), and chimeric sCD4 derivatives, such as CD4-IgG and CD4-PE40; blockers of HIV **RNaseH** activity, such as the AZT derivative azidothymidine monophosphate; drugs that alter the intracellular milieu to create conditions less favorable for. . .

US PAT NO: 5,612,034 [IMAGE AVAILABLE] L10: 23 of 28

SUMMARY:

BSUM(37)

Host . . . II, and non-classical class I HLA (E, F and G) for modulating immunoregulation, soluble T or B cell surface proteins, **cytokines**, interleukins and growth factors, such as individually IL1-16, soluble IL2 receptor, M-CSF, G-CSF, GM-CSF, platelet derived growth factor, alpha, beta,. . . complement factors, PAF aceter, ions such as calcium, potassium, magnesium, aluminum, iron, etc, enzymes such as proteases, kinases, phosphatases, DNAses, **RNAses**, lipases and other enzymes affecting cholesterol and other lipid metabolism, esterases, dehydrogenases, oxidases, hydrolases, sulphatases, cyclases, transferases, transaminases, atriopeptidases, carboxylases. . .

US PAT NO: 5,587,300 [IMAGE AVAILABLE] L10: 24 of 28

DETDESC:

DETD(6)

The . . . Mutant mRNAs can also be radiolabeled in vitro and used in RNA gel mobility shift assays, which involve transcribing radiolabeled **cytokine** RNAs in vitro by T7 RNA polymerase and incubating the products with cytosolic lysate derived from activated peripheral blood mononuclear cells or Jurkat cells under appropriate ionic conditions. After 10 minutes, **RNAse** T1 is added to cleave unprotected probe RNA followed by native or SDS-PAGE. AUBF-RNA complexes migrate with an

aggregate molecular. . .

US PAT NO: 5,550,111 [IMAGE AVAILABLE] L10: 25 of 28

SUMMARY:

BSUM(63)

The pathway involves the activation by 2-5A of the latent endoribonuclease, **RNase** L (EC 3.1.27). According to that pathway shown in FIG. 1, 2-5A is synthesized from ATP by 2', 5'-oligoadenylate synthetase. . . 2-5A exerts its biological effects by binding to and activating its only known target enzyme, the unique 2-5A dependent endoribonuclease **RNase** L. The latter cleaves viral and cellular mRNA or rRNA, thereby inhibiting protein synthesis. Hovanessian et al., Eur. J. Biochem.. . . bioactive 2-5A is inactivated by three enzymes: a relatively unspecific 2'-phosphodiesterase, a 5'-phosphatase, and a relatively specific 2', 3'-exonuclease. Some **cytokines**, e.g. IL-6, activate 2-5A synthetase in such a way as to cause the enzyme or particular forms of the enzyme. . . bioinactive forms of 2-5A (Bickel, M., Dveksler, G, Dieffenbach, C., W., Ruhl, S., Midura, S., B. and Pluznik, D. H., **Cytokine** 2:238-246 (1990) and Cohen, B., Gothelf, Y., Vaiman, D., Revel, M. and Chebath, J., **Cytokine** 3:83-91 (1991)).

SUMMARY:

BSUM(67)

The 2-5A synthetase/**RNase** L system as an antiviral cellular defense mechanism has been shown to be a promising target for antiviral chemotherapy, particularly. . . authentic 2-5A. What is needed is a method for controlling HIV, chronic fatigue caused by HBLV, and other viral or **cytokine**-induced disease states characterized by a 2-5A pathway defect using compounds that are more metabolically stable and active than authentic 2-5A.. . .

US PAT NO: 5,510,461 [IMAGE AVAILABLE] L10: 26 of 28

DETDESC:

DETD(14)

The . . . response in a cell. For example, an agent can be a small organic molecule, a biological response modifier (e.g., a **cytokine**) or a molecule which can crosslink surface structures on the cell (e.g., an antibody). Expression of pp32 mRNA in a. . . pp32 cDNA, e.g., SEQ ID NO: 1). Alternatively, pp32 mRNA can be detected by standard hybridization techniques (e.g., Northern hybridization; **RNase** protection) using probes encompassing all or part of a nucleotide sequence encoding a pp32 protein (e.g., all or part of. . .

US PAT NO: 5,241,051 [IMAGE AVAILABLE] L10: 27 of 28

DETDESC:

DETD(51)

Oncoinhibin is stable to both acidic and alkaline conditions at a pH range of 2.0-10.0 (Table VIII). Several **cytokines** have been reported which are stable to pH 2, including IFN-.alpha., IFN-.beta., IL-2, IL-4, IL-8, CSF-1, GM-CSF, TGF-.beta., Oncostatin M. . . . A375 melanoma cell line which is stable to heat 96.degree. C. for 10 minutes), protease K (10 .mu.g/ml), trypsin, pronase, **RNase**, DNase and periodate oxidation. LPF can be precipitted by trichloroacetic acid (10%) without any loss of biological activity. Oncoinhibin was. . .

US PAT NO: 5,202,116 [IMAGE AVAILABLE] L10: 28 of 28

SUMMARY:

BSUM(62)

A . . . (Polverini and Novak, 1986, Biochem. Biophys. Res. Comm. 140: 90), angiostatic steroids (Ingber et al., 1986, Endocrinol. 119: 1768), placental **RNAse** inhibitor (Shapiro and Vallee, 1987, Proc. Natl. Acad. Sci. USA 84: 2238), as well as a variety of compounds which influence matrix synthesis and integrity (Ingber and Folkman, 1988, Lab. Invest. 59: 44). Certain **cytokines** also demonstrate angiostatic activities including IFN-.gamma., TNF-.alpha. and TGF-.beta., all of which have been shown to block the proliferative response. . . al., in Current Comminications in Molecular Biology, 119-124, Rifkin and Klagsbrun, Eds., Cold Spring Harbor Press 1987). However, when these **cytokines** were tested in rabbit corneal neovascularization assays, they exhibited angiogenic activity, a response thought to result from the chemotactic effects of these **cytokines** on inflammatory leukocytes involved in the release of angiogenic factors (Freter-Schroder et al., 1987, Proc. Natl. Acad. Sci. USA 84: 527). Another **cytokine**, interleukin-1 (IL-1) also demonstrates angiogenic properties in the rabbit eye anterior chamber model initiating inflammatory response as well as leukocyte. . .

=> s ribonuclease

L1 17303 RIBONUCLEASE

=> s l1 (p) onconase

L2 19 L1 (P) ONCONASE

=> s onconase

L3 58 ONCONASE

=> s l3 (p) (conjugat? or chimera? or derivativ? or hybrid? or fus?)

L4 18 L3 (P) (CONJUGAT? OR CHIMERA? OR DERIVATIV? OR HYBRID? OR FUS?)

=> d l4 1-18 kwic

L4 ANSWER 8 OF 18 CAPLUS COPYRIGHT 1998 ACS
IT 9001-99-4D, ***Onconase*** , ***conjugates***
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as cytotoxins; specific targetting of toxins or radionuclides to tumor cells using ***conjugates*** with cytokines and bispecific antibodies recognizing cell surface marker and cytokine)

L4 ANSWER 12 OF 18 CAPLUS COPYRIGHT 1998 ACS
AB ***Onconase*** is a cytotoxic RNase with antitumor properties. A semisynthetic gene encoding the entire protein sequence was constructed by ***fusing*** oligonucleotides coding for the first 15 and last six of the 104 amino acid residues to a genomic clone that encoded the remaining amino acid residues. Addnl., the 15 N-terminal amino acid residues of ***onconase*** were replaced with the first 21 amino acid residues of the homologous human RNase, eosinophil-derived neurotoxin, EDN. Two versions of the ***hybrid*** EDN- ***onconase*** protein were cloned, expressed and purified. The ***chimera*** that contained a glycine in lieu of the aspartic acid present in native ***onconase*** (position 26 in the ***chimera***) exhibited enzymic activity more characteristic of EDN than native ***onconase*** and was considerably more active with respect to both RNase activity and cellular cytotoxicity than recombinant ***onconase*** . In contrast to native or recombinant ***onconase*** , the EDN ***chimera*** was recognized by anti-EDN polyclonal antibodies, demonstrating that the ***chimera*** also shared structural antigenic determinants to the human enzyme. These results demonstrate that a chimeric RNase has cytotoxicity comparable to ***onconase*** in two out of four cell lines tested. The implications with regard to cancer therapy are presented.
IT Cytokines
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(EDN (eosinophil-derived neurotoxin), ***fusion*** products with ***onconase*** ; expression and characterization of cytotoxic human-frog chimeric RNase and its potential for cancer therapy)
IT ***Fusion*** proteins (chimeric proteins)
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(eosinophil-derived neurotoxin- ***onconase*** ; expression and characterization of cytotoxic human-frog chimeric RNase and its potential for cancer therapy)
IT 9001-99-4DP, ***Onconase*** , ***fusion*** products
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(expression and characterization of cytotoxic human-frog chimeric RNase and its potential for cancer therapy)

L4 ANSWER 13 OF 18 CAPLUS COPYRIGHT 1998 ACS
AB . . . are useful lead compds. for the design of drugs to control tumor angiogenesis, allergic reactions, and viral replication. One RNase (***Onconase***) and several RNase activators are now in clin. trials for cancer treatment or inhibition of chronic virus infections. Several others, alone or ***conjugated*** with specific cell binding mols., are being developed for their antifungal, antiviral, and antitumor cell activity.

L4 ANSWER 14 OF 18 CAPLUS COPYRIGHT 1998 ACS
AB . . . immunodeficiency virus type I (HIV-1) infection of H9 cells. We now report that an RNase homologous to RNase A, named ***onconase*** , inhibits virus replication in chronically HIV-1-infected human cells without killing the virally infected cell. Examg. the mechanism of this inhibition shows that ***onconase*** enters the infected cells and degrades HIV-1 RNA without degrading rRNA or the three different cellular mRNAs analyzed. The homologous human pancreatic RNase lacks anti-viral activity. Comparing recombinant forms of ***onconase*** and a ***onconase*** -human RNase ***chimera*** shows that the N-terminal 9 amino acids and the pyroglutamyl residue of ***onconase*** are required for full anti-viral activity. Thus, extracellular RNases can enter cells, metabolize select RNAs, and inhibit HIV virion prodn.. . .

L4 ANSWER 15 OF 18 CAPLUS COPYRIGHT 1998 ACS
AB ***Onconase*** , a RNase isolated from Rana pipiens oocytes and early embryos, is a member of the RNase A superfamily. ***Onconase*** has anti-neoplastic properties both in vitro and in vivo, and is undergoing clin. evaluation. In the present study, ***Onconase*** was combined with or ***conjugated*** to MRK16, an anti-P-glycoprotein (Pgp) monoclonal antibody. The interaction of these combinations with vincristine (VCR) against parental and multi-drug resistant. . . of athymic nude mice given transplants of drug resistant HT-29mdr1 cells in vivo. The results suggest that combination treatment with ***Onconase*** and other agents that modulate the chemosensitivity of Pgp-expressing human tumor cells has the potential to overcome MDR.

L4 ANSWER 16 OF 18 CAPLUS COPYRIGHT 1998 ACS
AB . . . high enzyme activity, extreme sensitivity to RNase inhibitor (RI) and is non-toxic, whereas a homologous RNase from frog eggs, called ***onconase*** , has much lower enzyme activity, is not sensitive to RI and is cytotoxic to cancer cell lines and animals. To explore the structural basis of these differences among members in the RNase family we synthesized genes for ***onconase*** , hRNase, a mutant ***onconase*** (K9Q) and ***onconase*** -hRNase N-terminal ***hybrids*** and expressed the proteins in Escherichia coli with final yields of 10 to 50 mg per L of culture after purifn. A recombinant version of ***onconase*** with an N-terminal methionine instead of the native pyroglutamyl residue had decreased cytotoxicity and enzyme activity. Cleavage of the recombinant ***onconase*** Met-1 residue, and cyclization of the Gln1 residue to reform the pyroglutamyl N terminus, reconstituted cytotoxicity and enzyme activity. Thus. . . of the pyroglutamyl residue in the active site of amphibian RNases is indicated. Replacement of one to nine residues of ***onconase*** with the homologous residues of hRNase increased the enzymic activity against most of the substrates tested with a simultaneous shift in the enzyme specificity from high preference for poly(U) to slight preference for poly(C). Cytotoxicity of the ***chimera*** decreased, dissocg. cytotoxicity from enzymic activity. The mol. basis for the low binding affinity of ***onconase*** for RI has been examd. exptl. with the recombinant RNases and by fitting ***onconase*** and RNase A structures to the coordinates from the recently published RNase A-RI complex.

L4 ANSWER 17 OF 18 CAPLUS COPYRIGHT 1998 ACS
TI Cytotoxic ***onconase*** and ribonuclease A ***chimeras*** : comparison and in vitro characterization
AB ***Onconase*** , a protein isolated from fertilized Rana pipiens eggs, has antineoplastic properties both in vitro and in vivo. The protein is a member of the pancreatic RNase A superfamily. Previous work has demonstrated that bovine pancreatic RNase A ***conjugated*** to transferrin or antibodies to the human transferrin receptor acted like immunotoxins to specifically inhibit protein synthesis in ligand-pos. cells and prevent the growth of human glioblastoma tumors in vivo. To explore the properties of ***onconase*** as an immunotoxin, this RNase A homolog was ***conjugated*** to transferrin or an antibody (5E-9) to the human transferrin receptor, and its activity was compared with that of bovine pancreatic RNase A ***conjugates*** . The IC50 values of both the ***onconase*** and the RNase A ***conjugates*** as inhibitors of protein synthesis in K562 human erythroleukemia cells were in the nanomolar range. Unconjugated ***onconase*** also inhibited protein synthesis in K562 cells but was 20-100-fold less toxic on a molar basis than the ***onconase*** ***conjugates*** . The time course profiles of ***onconase*** and ***onconase*** ***conjugates*** in affecting protein and RNA synthesis were very similar. Inhibition of protein synthesis was preceded by a decrease in RNA synthesis that subsequently increased relative to control values before it decreased again with time. ***Conjugated*** ***onconase*** entered cells via a route mediated by transferrin or 5E-9, since excess of either ligand blocked toxicity of the ***conjugate*** but not the toxicity of unconjugated ***onconase*** . ***Conjugated*** ***onconase*** could also enter cells via the ***onconase*** portion of the ***conjugate*** , since it inhibited protein synthesis in cells that are not recognized by anti-human transferrin receptor antibody. ASPC-1 pancreatic carcinoma cells were essentially resistant to ***onconase*** alone, as measured by cell viability; however, when ***conjugated*** to antibody, ***onconase*** did decrease the viability of ASPC-1 cells. This

effect was markedly increased when the ***onconase*** ***conjugate*** was combined with tamoxifen. These results demonstrate that the cytotoxic properties of a member of the RNase A superfamily with inherent antitumor effects can be enhanced by ***conjugation*** to ligands capable of internalization.
ST ***onconase*** RNase ***conjugate*** antitumor
IT Transcription, genetic
Translation, genetic
(by neoplasm, ***onconase*** and RNase A ***conjugates*** inhibition of)
IT Neoplasm inhibitors
(***onconase*** and RNase A ***conjugates*** as)
IT Antibodies
RL: BIOL (Biological study)
(to transferrin receptors, ***onconase*** and RNase A ***conjugates*** with, neoplasm inhibition by)
IT Transferrins
RL: BIOL (Biological study)
(***conjugates*** , with ***onconase*** and RNase, neoplasm inhibition by)
IT Transferrins
RL: BIOL (Biological study)
(receptors, antibodies to, ***onconase*** and RNase A ***conjugates*** with, neoplasm inhibition by)
IT Receptors
RL: BIOL (Biological study)
(transferrin, antibodies to, ***onconase*** and RNase A ***conjugates*** with, neoplasm inhibition by)
IT 9001-99-4D, RNase A, conjugates 133737-96-9D, ***Onconase*** , ***conjugates***
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibition by)
IT 10540-29-1, Tamoxifen
RL: BIOL (Biological study)
(neoplasm inhibition by ***onconase*** ***conjugates*** potentiation by)

L4 ANSWER 18 OF 18 CAPLUS COPYRIGHT 1998 ACS
AB ***Onconase*** , or P-30, is a protein initially purified from exts. of Rana pipiens oocytes and early embryos based upon its anticancer. . . protein with an apparent mol. mass of 12,000 daltons and is homologous to RNase A. In cultured 9L glioma cells, ***onconase*** inhibits protein synthesis with an IC50 of about 10-7 M. The inhibition of protein synthesis correlates with cell death detd. by clonogenic assays. 125I-Labeled ***onconase*** binds to specific sites on cultured 9L glioma cells. Scatchard anal. of the binding data shows that ***onconase*** appears to bind to cells with two different affinities, one with a Kd of 6.2 x 10-8 and another of 2.5 x 10-7 M. Each cell could bind about 3 x 105 mols. of ***onconase*** at each of the two affinity sites. The low affinity Kd is similar to the IC50 for ***onconase*** toxicity. ***Onconase*** also demonstrates a saturability of cytotoxicity at a concn. that would sat. the low affinity binding site. Incubation at 4.degree. increased the binding of ***onconase*** to cells relative to 37.degree. binding and also increased the sensitivity of cells to ***onconase*** toxicity, indicating that receptor binding may be an initial step in cell toxicity. ***Onconase*** cytotoxicity can be blocked by metabolic inhibitors, NaN3 and 2-deoxyglucose, and cytotoxicity is potentiated 10-fold by monensin. RNase activity appears necessary for ***onconase*** toxicity because alkylated ***onconase*** , which only retains 2% of the RNase activity, was at least 100-fold less potent in inhibiting protein synthesis in cells. ***Onconase*** inhibition of protein synthesis in 9L cells coincides with the degrdn. of cellular 28 S and 18 S rRNA. In contrast to RNase A, ***onconase*** is resistant to two RNase inhibitors, placental RNase inhibitor and Inhibit-AceTM. Northern ***hybridization*** with placental RNase inhibitor cDNA probe indicates that 9L glioma cells contain endogenous placental RNase inhibitor mRNA. Based on these results, we propose that ***onconase*** toxicity results from ***onconase*** binding to cell surface receptors, internalization to the cell cytosol where it degrades rRNA, inhibiting protein synthesis and causing cell. . .

=> d his

(FILE 'HOME' ENTERED AT 14:20:34 ON 18 SEP 1998)

FILE 'MEDLINE, CAPLUS' ENTERED AT 14:23:23 ON 18 SEP 1998
L1 17303 S RIBONUCLEASE
L2 19 S L1 (P) ONCONASE
L3 58 S ONCONASE
L4 18 S L3 (P) (CONJUGAT? OR CHIMERA? OR DERIVATIV? OR HYBRID?

=> d l4 1-18 cit

'CIT' IS NOT A VALID FORMAT
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REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):bib

L4 ANSWER 1 OF 18 MEDLINE
AN 1998215642 MEDLINE
DN 98215642
TI Single amino acid substitutions at the N-terminus of a recombinant cytotoxic ribonuclease markedly influence biochemical and biological properties.
AU Newton D L; Boque L; Wlodawer A; Huang C Y; Rybak S M
CS Intramural Research Support Program, SAIC Frederick, Macromolecular Structure Laboratory, ABL-Basic Research Program, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD 21702, USA.
SO BIOCHEMISTRY, (1998 Apr 14) 37 (15) 5173-83.
Journal code: A0G. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199807
EW 19980703

L4 ANSWER 2 OF 18 MEDLINE
AN 1998149587 MEDLINE
DN 98149587
TI Ribonucleases protect RNA from acid precipitation.
AU Kouretas D; Antonoglou O
CS Laboratory of Pharmacology, School of Veterinary Medicine, University of Thessaly, Karditsa, Greece.
SO CELLULAR AND MOLECULAR BIOLOGY, (1997 Dec) 43 (8) 1181-90.
Journal code: BNA.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199806
EW 19980604

L4 ANSWER 3 OF 18 MEDLINE
AN 97337432 MEDLINE
DN 97337432
TI Expression and characterization of a cytotoxic human-frog chimeric ribonuclease: potential for cancer therapy.
AU Newton D L; Xue Y; Boque L; Wlodawer A; Kung H F; Rybak S M
CS Intramural Research Support Program, SAIC Frederick, National Cancer Institute-Frederick Cancer Research and Development Center, MD 21702, USA.
SO PROTEIN ENGINEERING, (1997 Apr) 10 (4) 463-70.
Journal code: PR1. ISSN: 0269-2139.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
EW 19971004

L4 ANSWER 4 OF 18 MEDLINE
AN 97325521 MEDLINE
DN 97325521
TI From housekeeper to microsurgeon: the diagnostic and therapeutic potential of ribonucleases [published erratum appears in Nat Biotechnol 1997 Oct;15(10):927].
AU Schein C H
CS University of Texas Medical Branch, Galveston 77546-1157, USA.. werner@nmr.utmb.edu
SO NATURE BIOTECHNOLOGY, (1997 Jun) 15 (6) 529-36. Ref: 115
Journal code: CQ3. ISSN: 1087-0156.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199710

L4 ANSWER 5 OF 18 MEDLINE
AN 96355422 MEDLINE
DN 96355422
TI Inhibition of HIV-1 production and selective degradation of viral RNA by an amphibian ribonuclease.
AU Saxena S K; Gravell M; Wu Y N; Mikulski S M; Shogen K; Ardelt W; Youle R J
CS Biochemistry Section of the Surgical Neurology Branch, NINDS, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Aug 23) 271 (34) 20783-8.
Journal code: HIV. ISSN: 0021-9258.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199612

L4 ANSWER 6 OF 18 MEDLINE
AN 96192084 MEDLINE
DN 96192084
TI Role of the N terminus in RNase A homologues: differences in catalytic activity, ribonuclease inhibitor interaction and cytotoxicity.
AU Boix E; Wu Y; Vasandani V M; Saxena S K; Ardelt W; Ladner J; Youle R J
CS National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA.
SO JOURNAL OF MOLECULAR BIOLOGY, (1996 Apr 19) 257 (5) 992-1007. Journal code: J6V. ISSN: 0022-2836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199609

L4 ANSWER 7 OF 18 MEDLINE
AN 93252963 MEDLINE
DN 93252963
TI A cytotoxic ribonuclease. Study of the mechanism of onconase cytotoxicity.
AU Wu Y; Mikulski S M; Ardelt W; Rybak S M; Youle R J
CS Biochemistry Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 May 15) 268 (14) 10686-93. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199308

L4 ANSWER 8 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1998:251079 CAPLUS
DN 128:304043
TI Specific targetting of toxins or radionuclides to tumor cells using conjugates with cytokines and bispecific antibodies recognizing a cell surface marker and the cytokine
IN Goldenberg, David M.
PA Immunomedics, Inc., USA; Goldenberg, David M.
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
PI WO 9816254 A1 980423
DS W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 97-US17924 971014
PRAI US 96-28430 961017
DT Patent
LA English

L4 ANSWER 9 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1998:248833 CAPLUS
DN 129:51330
TI Single amino acid substitutions at the N-terminus of a recombinant cytotoxic ribonuclease markedly influence biochemical and biological properties
AU Newton, Dianne L.; Boque, Lluis; Wlodawer, Alexander; Huang, Charles Y.; Rybak, Susanna M.
CS Intramural Research Support Program, Macromolecular Structure Laboratory, ABL-Basic Research Program, SAIC Frederick, Frederick, MD, 21702, USA
SO Biochemistry (1998), 37(15), 5173-5183
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
OS CJACS-IMAGE; CJACS

L4 ANSWER 10 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1998:77665 CAPLUS
DN 128:241103
TI Ribonucleases protect RNA from acid precipitation
AU Kouretas, Demetrios; Antonoglou, Orpheus
CS Laboratory of Pharmacology, School of Veterinary Medicine, University of Thessaly, Karditsa, 43100, Greece
SO Cell. Mol. Biol. (Paris) (1997), 43(8), 1181-1190
CODEN: CMOBEF; ISSN: 0145-5680
PB C.M.B. Association
DT Journal
LA English

L4 ANSWER 11 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1997:684506 CAPLUS
DN 127:343335
TI Amino acid-substituted analogs of the cytostatic, cytotoxic ribonuclease Onconase that can be manufactured on a large scale
IN Youle, Richard J.; Vasandani, Veena M.; Wu, You-neng; Boix, Ester; Ardelt, Wojciech
PA Youle, Richard J., USA; Vasandani, Veena M.; Wu, You-Neng; Boix, Ester; Ardelt, Wojciech; United States Dept. of Health and Human Services
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
PI WO 9738112 A1 971016
DS W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 97-US5675 970404
PRAI US 96-626288 960404
DT Patent
LA English

L4 ANSWER 12 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1997:396299 CAPLUS
DN 127:132533
TI Expression and characterization of a cytotoxic human-frog chimeric ribonuclease: potential for cancer therapy
AU Newton, Dianne L.; Xue, Ying; Boque, Lluis; Wlodawer, Alexander; Kung, Hsiang Fu; Rybak, Susanna M.
CS Intramural Research Support Program, SAIC Frederick, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD, 21702, USA
SO Protein Eng. (1997), 10(4), 463-470
CODEN: PRENE9; ISSN: 0269-2139
PB Oxford University Press
DT Journal
LA English

L4 ANSWER 13 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1997:370874 CAPLUS
DN 127:77670
TI From housekeeper to microsurgeon: The diagnostic and therapeutic potential of ribonucleases
AU Schein, Catherine H.
CS Structural Biology, Univ. Texas Med. Branch, Galveston, TX, 77546-1157, USA
SO Nat. Biotechnol. (1997), 15(6), 529-536
CODEN: NABIF9; ISSN: 1087-0156
PB Nature America
DT Journal; General Review
LA English

L4 ANSWER 14 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1996:528435 CAPLUS
DN 125:189161
TI Inhibition of HIV-1 production and selective degrdn. of viral RNA by an amphibian ribonuclease
AU Saxena, Shailendra K.; Gravell, Maneth; Wu, You-Neng; Mikulski, Staislaw M.; Shogen, Kuslima; Ardelt, Wojciech; Youle, Richard J.
CS Biochem. Section of the Surgical Neurology Branch, National Inst. Health, Bethesda, MD, 20892, USA
SO J. Biol. Chem. (1996), 271(34), 20783-20788
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

L4 ANSWER 15 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1996:373713 CAPLUS
DN 125:48624
TI Anti-tumor ribonuclease, combined with or conjugated to monoclonal antibody MRK16, overcomes multidrug resistance to vincristine in vitro and in vivo
AU Newton, Dianne L.; Pearson, John W.; Xue, Ying; Smith, Mark R.; Fogler, William E.; Mikulski, Stanislaw M.; Alvord, W. Gregory; Kung, Hsiang-Fu; Longo, Dan L.; Rybak, Susanna M.
CS BCDP, SAIC, Frederick, MD, 21702, USA
SO Int. J. Oncol. (1996), 8(6), 1095-1104
CODEN: IJONES; ISSN: 1019-6439
DT Journal
LA English

L4 ANSWER 16 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1996:246769 CAPLUS

DN 124:336617
TI Role of the N terminus in RNase A homologs: differences in catalytic activity, ribonuclease inhibitor interaction and cytotoxicity
AU Boix, Ester; Wu, YouNeng; Vasandani, Veena M.; Saxena, Shailendra K.; Ardelt, Wojciech; Ladner, Jane; Youle, Richard J.
CS Biochem. Section Surgical Neurology Branch, Natl. Inst. Neurol. Disorders Stroke, Natl. Inst. Health, Bethesda, MD, 20892, USA
SO J. Mol. Biol. (1996), 257(5), 992-1007
CODEN: JMOBAK; ISSN: 0022-2836
DT Journal
LA English

L4 ANSWER 17 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1994:235592 CAPLUS
DN 120:235592
TI Cytotoxic ***onconase*** and ribonuclease A ***chimeras*** : comparison and in vitro characterization
AU Rybak, Susanna M.; Newton, Dianne L.; Mikulski, Stanislaw M.; Viera, Al; Youle, Richard J.
CS Surg. Neurol. Branch, Natl. Inst. Neurol. Dis. Stroke, Bethesda, MD, 20892, USA
SO Drug Delivery (1993), 1(1), 3-10
CODEN: DDELEB; ISSN: 1071-7544
DT Journal
LA English

L4 ANSWER 18 OF 18 CAPLUS COPYRIGHT 1998 ACS
AN 1993:420099 CAPLUS
DN 119:20099
TI A cytotoxic ribonuclease. Study of the mechanism of onconase cytotoxicity
AU Wu, You Neng; Mikulski, Stanislaw M.; Ardelt, Wojciech; Rybak, Susanna M.; Youle, Richard J.
CS Surg. Neurol. Branch, Natl. Inst. Neurol. Disord. Stroke, Bethesda, MD, 20892, USA
SO J. Biol. Chem. (1993), 268(14), 10686-93
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

=> s l4 (p) (cytokin?)

L5 2 L4 (P) (CYTOKIN?)

=> d l5 1-2 bib ab

L5 ANSWER 1 OF 2 CAPLUS COPYRIGHT 1998 ACS
AN 1998:251079 CAPLUS
DN 128:304043
TI Specific targetting of toxins or radionuclides to tumor cells using conjugates with cytokines and bispecific antibodies recognizing a cell surface marker and the cytokine
IN Goldenberg, David M.
PA Immunomedics, Inc., USA; Goldenberg, David M.
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
PI WO 9816254 A1 980423
DS W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 97-US17924 971014
PRAI US 96-28430 961017
DT Patent
LA English
AB Methods for treatment of B-cell malignancies that make use of slowly internalizing surface antigens and that increase the stability of binding of antibodies to the surfaces of lymphomas are described. This is achieved using conjugates of toxins or radionuclides with interleukin 15 in combination with bispecific antibodies that recognize the .alpha.-chain of interleukin 15 and a malignant cell marker. The interleukin 15 receptor can be bridged to a slowly internalizing surface antigens using the bispecific antibody to introduce cytotoxins into cells bearing the antigen and the receptor.

L5 ANSWER 2 OF 2 CAPLUS COPYRIGHT 1998 ACS
AN 1997:396299 CAPLUS
DN 127:132533
TI Expression and characterization of a cytotoxic human-frog chimeric ribonuclease: potential for cancer therapy
AU Newton, Dianne L.; Xue, Ying; Boque, Lluis; Wlodawer, Alexander; Kung, Hsiang Fu; Rybak, Susanna M.
CS Intramural Research Support Program, SAIC Frederick, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD, 21702, USA
SO Protein Eng. (1997), 10(4), 463-470
CODEN: PRENE9; ISSN: 0269-2139
PB Oxford University Press
DT Journal
LA English
AB Onconase is a cytotoxic RNase with antitumor properties. A semisynthetic gene encoding the entire protein sequence was constructed by fusing oligonucleotides coding for the first 15 and last six of the 104 amino acid residues to a genomic clone that encoded the remaining amino acid residues. Addnl., the 15 N-terminal amino acid residues of onconase were replaced with the first 21 amino acid residues of the homologous human RNase, eosinophil-derived neurotoxin, EDN. Two versions of the hybrid EDN-onconase protein were cloned, expressed and purified. The chimera that contained a glycine in lieu of the aspartic acid present in native onconase (position 26 in the chimera) exhibited enzymic activity more characteristic of EDN than native onconase and was considerably more active with respect to both RNase activity and cellular cytotoxicity than recombinant onconase. In contrast to native or recombinant onconase, the EDN chimera was recognized by anti-EDN polyclonal antibodies, demonstrating that the chimera also shared structural antigenic determinants to the human enzyme. These results demonstrate that a chimeric RNase has cytotoxicity comparable to onconase in two out of four cell lines tested. The implications with regard to cancer therapy are presented.

=> d l5 1-2 kwic

L5 ANSWER 1 OF 2 CAPLUS COPYRIGHT 1998 ACS
IT 9001-99-4D, ***Onconase*** , ***conjugates***
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as cytotoxins; specific targetting of toxins or radionuclides to tumor cells using ***conjugates*** with ***cytokines*** and bispecific antibodies recognizing cell surface marker and ***cytokine***)

L5 ANSWER 2 OF 2 CAPLUS COPYRIGHT 1998 ACS
IT ***Cytokines***
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(EDN (eosinophil-derived neurotoxin), ***fusion*** products with ***onconase*** ; expression and characterization of cytotoxic human-frog chimeric RNase and its potential for cancer therapy)

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 ********************************
 *      WELCOME TO THE          *
 *   U.S. PATENT TEXT FILE      *
 ********************************

=> s onconase

L1        3 ONCONASE

=> s l1 (p) (conjugat? or derivativ? or hybrid? or fus?)

      48818 CONJUGAT?
     218485 DERIVATIV?
      50094 HYBRID?
     150094 FUS?
L2        3 L1 (P) (CONJUGAT? OR DERIVATIV? OR HYBRID? OR FUS?)

=> d l2 1-3 cit ab
```

1. 5,595,734, Jan. 21, 1997, Compositions comprising ONCONASE (tm) and lovastatin; Stanislaw M. Mikulski, et al., 424/94.6; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,595,734 [IMAGE AVAILABLE] L2: 1 of 3

ABSTRACT:
A pharmaceutical known by the trademark ONCONASE, as described in pending commonly owned application application number 07/436,141 filed Nov. 13, 1989, is combined with two forms of another drug known as Lovastatin. The combination of ONCONASE with Lovastatin has unexpected bioactivity in vitro against ASPC-1 human pancreatic adenocarcinoma cells, A-549 human lung carcinoma cells and HT-520 human squamous cell lung carcinoma cells.

2. 5,540,925, Jul. 30, 1996, Compositions comprising ONCONASE (TM) and STELAZINE (TM) or TAMOXIFEN (TM); Stanislaw M. Mikulski, et al., 424/94.6; 435/199; 514/12; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,540,925 [IMAGE AVAILABLE] L2: 2 of 3

ABSTRACT:
A pharmaceutical to be sold under the ONCONASE trademark, as described in pending commonly owned application application Ser. No. 07/436,141 filed Nov. 13, 1989 is combined with other drugs sold under the trademarks TAMOXIFEN and STELAZINE. The combination of ONCONASE with TAMOXIFEN has
unexpected bioactivity in vitro against ASPC-1 human pancreatic adenocarcinoma cells and the combination of ONCONASE with STELAZINE has unexpected bioactivity in vitro against A-549 human lung carcinoma cells.

3. 5,529,775, Jun. 25, 1996, Compositions comprising ONCONASE(.TM.) and cisplatin, melphalan, or doxorubicin HCl; Stanislaw M. Mikulski, et al., 424/94.6; 435/199; 514/12; 530/350 [IMAGE AVAILABLE]

US PAT NO: 5,529,775 [IMAGE AVAILABLE] L2: 3 of 3

ABSTRACT:
A pharmaceutical known by the trademark ONCONASE, as described in pending commonly owned application application Ser. No. 07/436,141 filed Nov. 13, 1989, is combined with drugs sold under the names cisplatin, Melphalan and Doxorubicin HCl. The combinations of ONCONASE with these drugs has unexpected bioactivity in vitro against OVCAR-3 human ovarian adenocarcinoma cells.

=> s (RNase#)

L1 37417 (RNASE#)

=> s l1 (p) (cytokine#)

L2 347 L1 (P) (CYTOKINE#)

=> s l2 (p) (conjugat? or hybrid# or fusion? or chimeric? or derivativ?)

L3 18 L2 (P) (CONJUGAT? OR HYBRID# OR FUSION? OR CHIMERIC? OR DERIVATI
V?)

=> d l3 1-18 bib ab

L3 ANSWER 1 OF 18 MEDLINE
AN 1998384185 MEDLINE
DN 98384185
TI A chimeric sperm peptide induces antibodies and strain-specific reversible infertility in mice.
AU Lea I A; van Lierop M J; Widgren E E; Grootenhuis A; Wen Y; van Duin M; O'Rand M G
CS Department of Cell Biology and Anatomy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA.
NC U54HD29099 (NICHD)
SO BIOLOGY OF REPRODUCTION, (1998 Sep) 59 (3) 527-36.
Journal code: A3W. ISSN: 0006-3363.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
EW 19981202
AB The development of a contraceptive vaccine based on a gamete-specific antigen requires knowledge of the ability of the antigen to elicit an immune response that inhibits fertilization. A well-defined immune response, as elicited by a synthetic peptide comprising a dominant B-cell epitope coupled to a common promiscuous T-cell epitope, might be preferable. In this study, the immunodominant B-cell epitope of sperm antigen Sp17 has been identified and synthesized as a ***chimeric*** peptide with the promiscuous T-cell epitope bovine ***RNase*** [94-104] at the N terminal. Immunization of female BALB/c mice with this peptide induced a dose-dependent reduction in fertility. Although antibodies to recombinant and native Sp17 were elicited in these mice, there was no strict correlation between the level of these antibodies and the reduction in fertility. Moreover, the induction of infertility was strain-specific since no effect on fertility could be induced in B6AF1 mice. To understand the mechanism behind this apparent strain-specific infertility induction, a more extended study on both the humoral and the cellular immune response to the ***chimeric*** peptide was performed. The antigen-specific T-cell response and the levels of antigen-specific ***cytokines*** are the major factors that affect fertility outcome.

L3 ANSWER 2 OF 18 MEDLINE
AN 1998114282 MEDLINE
DN 98114282
TI Exon-intron structure, analysis of promoter region, and chromosomal localization of the human type 1 sigma receptor gene.
AU Prasad P D; Li H W; Fei Y J; Ganapathy M E; Fujita T; Plumley L H; Yang-Feng T L; Leibach F H; Ganapathy V
CS Department of Biochemistry and Molecular Biology, Medical College of Georgia, Augusta 30912-2100, USA.
NC DA 10045 (NIDA)
SO JOURNAL OF NEUROCHEMISTRY, (1998 Feb) 70 (2) 443-51.
Journal code: JAV. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199804
EW 19980404
AB Sigma receptor is a protein that interacts with a variety of psychotomimetic drugs including cocaine and amphetamines and is believed to play an important role in the cellular functions of various tissues associated with the endocrine, immune, and nervous systems. Here we report on the structure and organization of the human gene coding for this receptor. The gene is approximately 7 kbp long and contains four exons, interrupted by three introns. Exon 3 is the shortest (93 bp), and exon 4 is the longest (1,132 bp). Among the introns, intron 3 is the longest (approximately 1,250 bp). Exon 2 codes for the single transmembrane domain present in the receptor. 5' rapid amplification of cDNA end reactions with mRNA from the JAR human trophoblast cell line have identified 56 bp upstream of the translation start codon as the initiation site for transcription. This transcription start site has been confirmed by ***RNase*** protection analysis. Structural analysis of the 5' flanking region has revealed that the gene is TATA-less. This region, however, contains a CCAATC box in the reverse complement and several GC boxes that are recognition sites for SP1. There are also consensus sequences for the liver-specific transcription factor nuclear factor-1/L, for a variety of ***cytokine*** responsive factors, and for the xenobiotic responsive factor called the arylhydrocarbon receptor. Southern blot analysis of the genomic DNA from Chinese hamster-human and mouse-human ***hybrid*** cell lines and fluorescent in situ hybridization with human metaphase chromosome spreads have shown that the gene is located on human chromosome 9, band p13, a region known to be associated with different psychiatric disorders.

L3 ANSWER 3 OF 18 MEDLINE
AN 94153574 MEDLINE
DN 94153574
TI Detection of rhinovirus infection of the nasal mucosa by oligonucleotide in situ hybridization.
AU Bardin P G; Johnston S L; Sanderson G; Robinson B S; Pickett M A; Fraenkel D J; Holgate S T
CS Immunopharmacology Group, Southampton General Hospital, United Kingdom.
SO AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, (1994 Feb) 10
(2) 207-13.
Journal code: AOB. ISSN: 1044-1549.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199406
AB Human rhinoviruses (HRVs) cause the common cold and often induce lower airway symptoms such as cough and wheezing. Although HRV infection is presumed to involve primarily ciliated epithelial cells, this has not been confirmed in vivo, and the cellular distribution and spread of infection as well as the pathogenesis of cold related nasal and chest symptoms remain speculative. We have developed in situ hybridization (ISH) to explore localization of the virus to airway tissues, employing HRV 16-derived oligonucleotide probes after sequencing part of the genome of this serotype. A reverse transcription-polymerase chain reaction was used to generate DNA from HRV 16 for sequencing; this yielded 305 nucleotide bases that showed considerable homology to other HRVs. The HRV 16 sequence was used to design oligonucleotides functioning as antisense and sense probes. These probes as well as random sequence and pathogen control oligonucleotides were applied to HRV-infected cell-clot complexes and finally to sections from six paired nasal biopsies obtained before, during, or after HRV-proven colds. Specificity of ***hybrids*** was established by the absence of signal in uninfected tissue, in cells infected with other viruses, after ***RNase*** pretreatment, and with application of control probes. Hybridization signals were observed in epithelial cells in three of six biopsies obtained during a cold, using probes to viral (+) strand; intermediate (-) strand, implying viral replication, was present in one biopsy. Evidence for infection of nonepithelial cells was inconclusive. HRVs cause productive infection of nasal epithelium during a cold and their intracellular localization may produce perturbation of inflammatory mediators and ***cytokine*** profiles.(ABSTRACT TRUNCATED AT 250 WORDS)

L3 ANSWER 4 OF 18 MEDLINE
AN 93016880 MEDLINE
DN 93016880
TI Human fibroblasts synthesize elevated levels of extracellular matrix proteins in response to interleukin 4.
AU Postlethwaite A E; Holness M A; Katai H; Raghow R
CS Division of Connective Tissue Diseases, University of Tennessee, Memphis 38163..
NC AR26034 (NIAMS)
AR39166 (NIAMS)
SO JOURNAL OF CLINICAL INVESTIGATION, (1992 Oct) 90 (4) 1479-85.
Journal code: HS7. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199301
AB Interleukin 4 (also known as "B cell stimulatory factor-1"), a ***cytokine*** product of T lymphocytes and mast cells, stimulates synthesis of the extracellular matrix proteins, types I and III collagen and fibronectin, by human dermal fibroblasts in vitro. Stimulation of collagen by human recombinant (hr)IL-4 was also demonstrated in several fibroblastic synovial cell lines obtained from patients with rheumatoid arthritis and osteoarthritis. The stimulatory effect of hrIL-4 on fibroblast collagen synthesis was specifically neutralized by rabbit anti-hrIL-4 Ig. IL-4 specifically increased the steady-state levels of types I and III procollagen and fibronectin mRNAs, with no effect on cytoplasmic beta-actin mRNA. Quantitative analysis of the levels of Pro alpha 1(I) collagen transcripts in IL-4-treated fibroblast cultures was also corroborated by antisense RNA-mRNA hybridization and ***RNAse*** resistant ***hybrids*** which showed that IL-4-treated fibroblasts expressed higher levels of Pro alpha 1(I) collagen transcripts. Nuclear run-off transcription experiments indicated that IL-4 stimulated the rates of mRNA biogenesis. Based on these observations we conclude that IL-4 exerts its effect on collagen and fibronectin synthesis at the pretranslational level, resulting in synthesis of these extracellular matrix proteins. These and other data suggest that IL-4 may be a

"fibrogenic ***cytokine*** " that could be important in promoting biogenesis of extracellular matrix proteins in normal wound healing and in pathological fibrosis in which mast cells and T lymphocytes play a central role.

L3 ANSWER 5 OF 18 MEDLINE
AN 91091519 MEDLINE
DN 91091519
TI Interleukin-6 mRNA and protein increase in vivo following induction of acute thrombocytopenia in mice.
AU Cox L H; Downs T; Dagg K; Henthorn J; Burstein S A
CS Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City..
NC HL29037 (NHLBI)
SO BLOOD, (1991 Jan 15) 77 (2) 286-93.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199104
AB Induction of experimental thrombocytopenia in rodents results in the enhancement of megakaryocytic growth and differentiation. Interleukin-3 (IL-3) and IL-6, ***cytokines*** with a broad spectrum of biologic activities, stimulate megakaryocytopoiesis in vitro. To determine if expression of these factors might increase in response to experimental thrombocytopenia, we measured steady-state levels of IL-3 and IL-6 mRNA following rabbit antiplatelet serum (APS) injection. Groups of mice were injected intravenously with 0.2 mL APS while control animals received rabbit antilymphocyte serum (ALS), normal rabbit serum (NRS), or phosphate-buffered saline (PBS). At various times up to 72 hours after injection mice were exsanguinated and splenectomized. Platelet counts in the experimental animals were less than 12% of controls. Splenic RNA was hybridized in solution to 32P-UTP-labeled cRNA probes for IL-3 and IL-6. ***RNase*** -resistant ***hybrids*** were resolved on denaturing gels and visualized autoradiographically. IL-3 ***hybrids*** were undetectable at all time points tested, irrespective of the film exposure time or specific activity of the probe. Conversely, IL-6 ***hybrids*** were easily visualized and showed peak expression at 1.5 to 2.0 hours. By 3 hours, IL-6 mRNA had returned almost to the level of the controls. Similar results were observed in the bone marrow, although maximal IL-6 mRNA in that tissue was observed 4 hours following APS administration. To determine if this mRNA increment was associated with a concomitant increase in bioactive protein, serum was tested for its ability to stimulate IL-6-dependent B9 cells. At 1.75 hours following injection, experimental animals showed a small but significant increment in IL-6 activity compared with controls (200 +/- 30 U/mL IL-6 compared with 129 +/- 17 U/mL in ALS-injected controls, 106 +/- 17 U/mL in NRS-injected controls and 84 +/- 17 U/mL in PBS-injected controls). The data show that IL-6 mRNA and bioactive protein increase in response to acute immunothrombocytopenia, while no increment in IL-3 is detectable. These results suggest that IL-6 may play a role in the physiologic response to acute immunothrombocytopenia.

L3 ANSWER 6 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1999:437594 CAPLUS
TI Characterization of UDP-glucuronosyltransferases active on steroid hormones
AU Hum, Dean W.; Belanger, Alain; Levesque, Eric; Barbier, Olivier; Beaulieu, Martin; Albert, Caroline; Vallee, Michel; Guillemette, Chantal; Tchernof, Andre; Turgeon, David; Dubois, Stephanie
CS Laboratory of Molecular Endocrinology, CHUL Research Center, Laval University, Quebec, PQ, G1V 4G2, Can.
SO J. Steroid Biochem. Mol. Biol. (1999), 69(1-6), 413-423
CODEN: JSBBEZ; ISSN: 0960-0760
PB Elsevier Science Ltd.
DT Journal
LA English
AB In recent years, the enzymes which are involved in the formation of DHT in steroid target tissues have been well investigated, however, enzymes responsible for the catabolism and elimination of steroids in these tissues, in particular the uridine diphosphoglucuronosyltransferase (UGT) family of enzymes, have received much less attention. We have recently demonstrated that human and monkey are unique in having high plasma levels of C19 steroid glucuronides. These circulating ***conjugates*** have been proposed to reflect the peripheral conversion of adrenal and gonadal C19 steroids to potent androgens, esp. DHT. In humans, the presence of steroid UGT activities is found in the liver and several extrahepatic tissues including the prostate, mammary gland and ovary. In addn., UGT activities were obsd. in breast and prostate tumor cell lines such as MCF-7 and LNCaP, resp. In agreement with the presence of steroid ***conjugating*** enzymes in extrahepatic tissues, UGT cDNA clones, which encode steroid ***conjugating*** proteins, have been isolated from libraries constructed from human and monkey prostate mRNA. The presence of UGT transcripts and proteins in extrahepatic tissues in both species, as detd. by Northern blot, ***RNase*** protection, specific RT-PCR, in situ hybridization, Western blot and immunocytochem. anal., indicate the relevance of steroid glucuronidation in tissues other than the liver. Knowing that both the human prostate and the human prostate cancer LNCaP cell line express steroid metabolizing proteins, including UGT enzymes, regulation of UGT mRNA and protein levels, as well as promoter activity was studied in these cells. The results demonstrate a differential regulation between the two highly related isoforms UGT2B15 and UGT2B17, where only the expression of UGT2B17 was affected following treatments of LNCaP cells with androgens, growth factors or ***cytokines*** . Steroid ***conjugation*** by UGT enzymes is potentially involved in hormone inactivation in steroid target tissues, thus modifications in UGT expression levels may influence hormonal responses.

L3 ANSWER 7 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1998:776602 CAPLUS
DN 130:20559
TI Selective cytotoxic reagents comprising RNase-active proteins fused to targeting antibodies
IN Rybak, Susanna M.; Youle, Richard J.; Newton, Dianne L.; Nicholls, Peter J.
PA United States Dept. of Health and Human Services, USA
SO U.S., 43 pp., Cont.-in-part of U.S. Ser. No. 14,082, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5840840	A	19981124	US 1993-125462	19930922
US 510696	A0	19910315	US 1990-510696	19900417
US 779195	A0	19921215	US 1991-779195	19911022
PRAI US 1990-510696		19900417		
US 1991-779195		19911022		
US 1993-14082		19930204		

AB The present invention relates to a selective cytotoxic RNase reagent. The reagent comprises a toxic moiety that is an RNase linked to a recognition moiety that binds a specific cell surface marker. Binding of the recognition moiety to a surface marker on a cell allows the toxic moiety to selectively kill the cell. To reduce immunogenicity, preferably the toxic moiety and the recognition moiety of the conjugate are endogenous to the species in which the reagent is intended for use. Cytotoxic reagents intended for use in humans preferably have as the toxic moiety a human RNase, such as angiogenin or eosinophil-derived neurotoxin, and as the recognition moiety a humanized chimeric antibody specific for human transferrin receptor. The human RNase and chimeric antibody preferably form a fused protein. The present invention also relates to pharmaceutical compns. including the cytotoxic reagent as well as treatment methods involving the use of the cytotoxic reagent.

L3 ANSWER 8 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1998:580771 CAPLUS
DN 129:288872
TI A chimeric sperm peptide induces antibodies and strain-specific reversible infertility in mice
AU Lea, I. A.; Lierop, M. J. C. Van; Widgren, E. E.; Grootenhuis, A.; Wen, Y.; Van Duin, M.; O'Rand, M. G.
CS Department of Cell Biology and Anatomy, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599, USA
SO Biol. Reprod. (1998), 59(3), 527-536
CODEN: BIREBV; ISSN: 0006-3363
PB Society for the Study of Reproduction
DT Journal
LA English
AB The development of a contraceptive vaccine based on a gamete-specific antigen requires knowledge of the ability of the antigen to elicit an immune response that inhibits fertilization. A well-defined immune response, as elicited by a synthetic peptide comprising a dominant B-cell epitope coupled to a common promiscuous T-cell epitope, might be preferable. In this study, the immunodominant B-cell epitope of sperm antigen Sp17 has been identified and synthesized as a ***chimeric*** peptide with the promiscuous T-cell epitope bovine ***RNase*** [94-104] at the N terminal. Immunization of female BALB/c mice with this peptide induced a dose-dependent redn. in fertility. Although antibodies to recombinant and native Sp17 were elicited in these mice, there was no strict correlation between the level of these antibodies and the redn. in fertility. Moreover, the induction of infertility was strain-specific since no effect on fertility could be induced in B6AF1 mice. To understand the mechanism behind this apparent strain-specific infertility induction, a more extended study on both the humoral and the cellular immune response to the ***chimeric*** peptide was performed. The antigen-specific T-cell response and the levels of antigen-specific ***cytokines*** are the major factors that affect fertility outcome.

L3 ANSWER 9 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1998:290199 CAPLUS
DN 129:53257
TI Effect of interleukins on UGT2B15 and UGT2B17 steroid uridine diphosphate-glucuronosyltransferase expression and activity in the LNCaP cell line
AU Levesque, Eric; Beaulieu, Martin; Guillemette, Chantal; Hum, Dean W.; Belanger, Alain
CS Medical Research Coucil Group in Molecular Endocrinology, CHUL Research Center, Laval University, Quebec, G1V 4G2, Can.

SO Endocrinology (1998), 139(5), 2375-2381
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
AB ***Cytokines*** are known to modulate the level of both phase 1 and phase 2 drug-metabolizing enzymes in hepatocytes. Although the effects of ***cytokines*** on cytochrome P 450(CYP450) enzymes are well understood, there is limited knowledge on how ***cytokines*** may affect steroid UDP-glucuronosyltransferase (UGT) phase 2 enzyme activity and expression in different cell types, including hepatocytes and steroid target cells. LNCaP cells, which is a human prostate cancer cell line, is a good model to study the effect of ***cytokines*** in steroid target cells because it is known to express steroidogenic enzymes, including UGT2B15 and UGT2B17, which are widely expressed steroid UGT enzymes known to ***conjugate*** androgens. In this study, we examd. the possible interaction among interleukin-1.alpha. (IL-1.alpha.), IL-4, IL-6, and steroid UGT enzymes (UGT2B15 and UGT2B17). Treatment of LNCaP cells with IL-1.alpha. led to a dose-dependent inhibition of dihydrotestosterone (DHT) glucuronidation. IL-1.alpha. decreased both UGT activity and LNCaP cell proliferation in the absence and presence of DHT (0.5 nM); a maximal inhibition of 70% was obsd. IL-6 inhibited LNCaP cell proliferation as well as the DHT-induced proliferation of these cells. However, neither IL-4 nor IL-6 significantly affected the formation of DHT glucuronide. ***RNase*** protection and Western blot analyses demonstrated a specific redn. of UGT2B17 transcript and protein levels in IL-1.alpha.-treated LNCaP cells. The level of UGT2B15 was not affected by ***cytokine*** treatments, indicating a differential regulation between these two UGT enzymes. Transfection expts. performed with the UGT2B17 gene promoter region indicates that the regulation occurs at the transcription level via putative cis-acting elements. This study indicates that cell proliferation and UGT expression in steroid-responsive cancer cells are differentially regulated depending on the ***cytokines*** present in the cell microenvironment.

L3 ANSWER 10 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1998:61260 CAPLUS
DN 128:213912
TI Exon - intron structure, analysis of promoter region, and chromosomal localization of the human type 1 .sigma. receptor gene
AU Prasad, Puttur D.; Li, Hui W.; Fei, You-Jun; Ganapathy, Malliga E.; Fujita, Takuya; Plumley, Lisa H.; Yang-Feng, Teresa L.; Leibach, Frederick H.; Ganapathy, Vadivel
CS Departments of Biochemistry and Molecular Biology, Medical College of Georgia, Augusta, GA, 30912-2100, USA
SO J. Neurochem. (1998), 70(2), 443-451
CODEN: JONRA9; ISSN: 0022-3042
PB Lippincott-Raven Publishers
DT Journal
LA English
AB .sigma. Receptor is a protein that interacts with a variety of psychotomimetic drugs including cocaine and amphetamines and is believed to play an important role in the cellular functions of various tissues assocd. with the endocrine, immune, and nervous systems. Here we report on the structure and organization of the human gene coding for this receptor. The gene is .apprx.7 kbp long and contains four exons, interrupted by three introns. Exon 3 is the shortest (93 bp), and exon 4 is the longest (1,132 bp). Among the introns, intron 3 is the longest (.apprx.1,250 bp). Exon 2 codes for the single transmembrane domain present in the receptor. 5' Rapid amplification of cDNA end reactions with mRNA from the JAR human trophoblast cell line have identified 56 bp upstream of the translation start codon as the initiation site for transcription. This transcription start site has been confirmed by ***RNase*** protection anal. Structural anal. of the 5' flanking region has revealed that the gene is TATA-less. This region, however, contains a CCAATC box in the reverse complement and several GC boxes that are recognition sites for SP1. There are also consensus sequences for the liver-specific transcription factor nuclear factor-1/L, for a variety of ***cytokine*** responsive factors, and for the xenobiotic responsive factor called the arylhydrocarbon receptor. Southern blot anal. of the genomic DNA from Chinese hamster-human and mouse-human ***hybrid*** cell lines and fluorescent in situ hybridization with human metaphase chromosome spreads have shown that the gene is located on human chromosome 9, band p13, a region known to be assocd. with different psychiatric disorders.

L3 ANSWER 11 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1997:396299 CAPLUS
DN 127:132533
TI Expression and characterization of a cytotoxic human-frog chimeric ribonuclease: potential for cancer therapy
AU Newton, Dianne L.; Xue, Ying; Boque, Lluis; Wlodawer, Alexander; Kung, Hsiang Fu; Rybak, Susanna M.
CS Intramural Research Support Program, SAIC Frederick, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD, 21702, USA
SO Protein Eng. (1997), 10(4), 463-470
CODEN: PRENE9; ISSN: 0269-2139
PB Oxford University Press
DT Journal
LA English
AB Onconase is a cytotoxic RNase with antitumor properties. A semisynthetic gene encoding the entire protein sequence was constructed by fusing oligonucleotides coding for the first 15 and last six of the 104 amino acid residues to a genomic clone that encoded the remaining amino acid residues. Addnl., the 15 N-terminal amino acid residues of onconase were replaced with the first 21 amino acid residues of the homologous human RNase, eosinophil-derived neurotoxin, EDN. Two versions of the hybrid EDN-onconase protein were cloned, expressed and purified. The chimera that contained a glycine in lieu of the aspartic acid present in native onconase (position 26 in the chimera) exhibited enzymic activity more characteristic of EDN than native onconase and was considerably more active with respect to both RNase activity and cellular cytotoxicity than recombinant onconase. In contrast to native or recombinant onconase, the EDN chimera was recognized by anti-EDN polyclonal antibodies, demonstrating that the chimera also shared structural antigenic determinants to the human enzyme. These results demonstrate that a chimeric RNase has cytotoxicity comparable to onconase in two out of four cell lines tested. The implications with regard to cancer therapy are presented.

L3 ANSWER 12 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1996:641888 CAPLUS
DN 125:294405
TI Complementary DNA for 12-kilodalton B cell growth factor: misassigned
AU Kovanen, Panu E.; Harju, Leena; Timonen, Tuomo
CS Haartman Inst., Univ. Helsinki, Helsinki, FIN-00014, Finland
SO Science (Washington, D. C.) (1996), 274(5287), 629-631
CODEN: SCIEAS; ISSN: 0036-8075
DT Journal
LA English
AB A genomic sequence anal. of genomic DNA for B-cell growth factor (BCGF) has revealed 4 errors in the published cDNA sequence, which resulted in a different open reading frame (ORF) within the 37 N-terminal amino acids. The ORF when translated as a glutathione S-transferase ***fusion*** protein has B-cell growth factor activity. To study the expression pattern of this 12-kDa BCGF, DNA and RNA probes were synthesized using the Alu-free portion of the BCGF nucleotide sequence. No BCGF-specific mRNA was detected in mitogen-stimulated human peripheral blood lymphocytes. Thus, mitogen-stimulated lymphocytes do not synthesize sufficient quantities of BCGF mRNA to be detected by Northern blot or by ***RNase*** protection analyses. This discrepancy with previous studies is probably explained by the unusual features of the sequence used in the previous study, namely the presence of Alu sequences. Thus, 12-kDa BCGF should be excluded from the continuously growing list of cloned ***cytokines*** .

L3 ANSWER 13 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1995:574426 CAPLUS
DN 123:29
TI Polyoxometalates in AIDS therapy
AU Clayette, Pascal; Dormont, Dominique
CS Experimental Neuropathogenesis and Neurovirology Laboratory, Commissariat a l'Energie Atomique, Fontenay aux Roses, 92265, Fr.
SO Top. Mol. Organ. Eng. (1994), 10, 387-400
CODEN: TMOEE7
DT Journal; General Review
LA English
AB A review with 63 refs. HIV causes a severe depletion of CD4-pos. helper T cells, and this predisposes patients to opportunistic infections and malignancies which are the leading reasons for morbidity and mortality in AIDS. The retroviral infection latency and immunol. abnormalities in patients might be established by the HIV infection of lymphocytes and monocytes/macrophages. In vitro various compds. have been reported for their ability to inhibit the HIV infection of lymphocytes. Among these and in regard of a large broad spectrum, polyoxometalates were evaluated regarding HIV infection inhibition. Polyoxometalates are polyanionic condensed oligomeric aggregates of transition metal ions, held together only by metal oxygen bonds. The results of in vitro and in vivo expts. revealed at least two mechanisms of action: (1) a direct inhibition of one (or more) of the phases of the lentiviral biol. cycle (binding, ***fusion*** , RT and ***RNase*** activities), (2) a modulation of the immune capacities (ADCC and NK functions) that might result in an restoration of the defective immune system of AIDS patients. Pharmacokinetic studies have been performed in human or non-human primates with two compds.: HPA-23, and JM-2820. These studies confirm (1) the extravascular distribution and (2) the long half-life of the metabolites of two mols. To date, HPA-23 is the only polyoxometalate for which development ended with clin. investigation. These short-term treatments did not permit to demonstrate any efficacy of in vivo HPA-23 administration. These data constitute preliminary elements to re-evaluate polyoxometalates. Indeed, three questions remain to be raised: (1) direct and/or indirect infection inhibition of macrophages, (2) the modulation of the ***cytokine*** network and (3) the efficiency of polyoxometalates in long-term treatment.

L3 ANSWER 14 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1994:596951 CAPLUS
DN 121:196951
TI Detection of rhinovirus infection of the nasal mucosa by oligonucleotide

in situ hybridization
AU Bardin, Philip G.; Johnston, Sebastian L.; Sanderson, Gwen; Robinson, B. Stephen; Pickett, Mark A.; Fraenkel, David J.; Holgate, Stephen T.
CS Immunopharmacol. Group, Southampton Gen. Hosp., Southampton, UK
SO Am. J. Respir. Cell Mol. Biol. (1994), 10(2), 207-13
CODEN: AJRBEL; ISSN: 1044-1549
DT Journal
LA English
AB Human rhinoviruses (HRVs) cause the common cold and often induce lower airway symptoms such as cough and wheezing. Although HRV infection is presumed to involve primarily ciliated epithelial cells, this has not been confirmed in vivo, and the cellular distribution and spread of infection as well as the pathogenesis of cold related nasal and chest symptoms remain speculative. In situ hybridization (ISH) was developed to explore localization of the virus to airway tissues, employing HRV 16-derived oligonucleotide probes after sequencing part of the genome of this serotype. A reverse transcription-polymerase chain reaction was used to generate DNA from HRV 16 for sequencing; this yielded 305 nucleotide bases that showed considerable homol. to other HRVs. The HRV 16 sequence was used to design oligonucleotides functioning as antisense and sense probes. These probes as well as random sequence and pathogen control oligonucleotides were applied to HRV-infected cell-clot complexes and finally to sections from 6 paired nasal biopsies obtained before, during, or after HRV-proven colds. Specificity of ***hybrids*** was established by the absence of signal in uninfected tissue, in cells infected tissue with other viruses, after ***RNase*** pretreatment, and with application of control probes. Hybridization signals were obsd. in epithelial cells in 3 of 6 biopsies obtained during a cold, using probes to viral (+) strand; intermediate (-) strand, implying viral replication, was present in one biopsy. Evidence for infection of nonepithelial cells was inconclusive. HRVs cause productive infection of nasal epithelium during a cold and their intracellular localization may produce perturbation of inflammatory mediators and ***cytokine*** profiles. Use of ISH will permit studies exploring the pathogenesis of HRV-related symptoms and clarification of the mechanisms of lower airway involvement.

L3 ANSWER 15 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1994:550016 CAPLUS
DN 121:150016
TI Isolation and chromosomal localization of the human endothelial nitric oxide synthetase (NOS3) gene
AU Robinson, Lisa J.; Weremowicz, Stanislawa; Morton, Cynthia C.; Michel, Thomas
CS Cardiovasc. Div., Brigham and Women's Hosp., Boston, MA, 02115, USA
SO Genomics (1994), 19(2), 350-7
CODEN: GNMCEP; ISSN: 0888-7543
DT Journal
LA English
AB Nitric oxide (NO) is an important intercellular signaling mol. synthesized in diverse human tissues by proteins encoded by a family of NO synthase (NOS) genes. The similarity of sequence and cofactor binding sites has suggested that the NOS genes may also be related to cytochrome P 450 reductase, as well as to plant and bacterial oxidoreductases. Endothelial NOS activity is a major determinant of vascular tone and blood pressure, and in several important (and sometimes hereditary) disease states, such as hypertension, diabetes, and atherosclerosis, the endothelial NO signaling system appears to be abnormal. To explore the relation of the endothelial NOS gene to other similar genes, and to delineate the genetic factors involved in regulating endothelial NOS activity, the authors isolated the human gene encoding the endothelial NOS. Genomic clones contg. the 5' end of this gene were identified in a human genomic library by applying a polymerase chain reaction (PCR)-based approach. Identification of the human gene for endothelial NOS (NOS3) was confirmed by nucleotide sequence anal. of the first coding exon, which was identical to its cognate cDNA. The NOS3 gene spans at least 20 kb and appears to contain multiple introns. The transcription start site and promoter region of the NOS3 gene were identified by primer extension and ***RNase*** protection assays. Sequencing of the putative promoter revealed consensus sequences for the shear stress-response element, as well as ***cytokine*** -responsive cis regulatory sequences, both possibly important to the roles played by NOS3 in the normal and the diseased cardiovascular system. The authors also mapped the chromosomal location of the NOS3 gene. First, a chromosomal panel of human-rodent somatic cell ***hybrids*** was screened using PCR with oligonucleotide primers derived from the NOS3 genomic clone. The specificity of the amplified PCR product was confirmed by human and hamster genomic DNA controls, as well as by Southern blot anal., using the NOS3 cDNA as probe. Definitive chromosomal assignment of the NOS3 gene to human chromosome 7 was based upon 0% discordancy; fluorescence in situ hybridization sublocalized the NOS3 gene to 7q36. The identification and characterization of the NOS3 gene may lead to further insights into heritable disease states assocd. with this gene product.

L3 ANSWER 16 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1993:5394 CAPLUS
DN 118:5394
TI Human fibroblasts synthesize elevated levels of extracellular matrix proteins in response to interleukin 4
AU Postlethwaite, Arnold E.; Holness, Maureen A.; Katai, Hitoshi; Raghow, Rajendra
CS Div. Connective Tissue Dis., Univ. Tennessee, Memphis, TN, 38163, USA
SO J. Clin. Invest. (1992), 90(4), 1479-85
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
AB Interleukin 4 (also known as B cell stimulatory factor-1), a ***cytokine*** product of T lymphocytes and mast cells, stimulates synthesis of the extracellular matrix proteins, types I and III collagen, and fibronectin, by human dermal fibroblasts in vitro. Stimulation of collagen by human recombinant (h)IL-4 was also demonstrated in several fibroblastic synovial cell lines obtained from patients with rheumatoid arthritis and osteoarthritis. The stimulatory effect of hrIL-4 on fibroblast collagen synthesis was specifically neutralized by rabbit anti-hrIL-4 Ig. IL-4 specifically increased the steady-state levels of types I and III procollagen and fibronectin mRNAs, with no effect on cytoplasmic .beta.-actin mRNA. Quant. anal. of the levels of Pro .alpha.1(I) collagen transcripts in IL-4-treated fibroblast cultures was also corroborated by antisense RNA-mRNA hybridization and ***RNAse*** resistant ***hybrids*** which showed that IL-4-treated fibroblasts expressed higher levels of Pro .alpha.1(I) collagen transcripts. Nuclear run-off transcription expts. indicated that IL-4 stimulated the rates of mRNA biogenesis. Thus, IL-4 exerts its effect on collagen and fibronectin synthesis at the pretranslation level, resulting in synthesis of these extracellular matrix proteins. These and other data suggest that IL-4 may be a fibrogenic ***cytokine*** that could be important in promoting biogenesis of extracellular matrix proteins in normal wound healing and in pathol. fibrosis in which mast cells and T lymphocytes play a central role.

L3 ANSWER 17 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1992:253627 CAPLUS
DN 116:253627
TI Detection of in vivo-induced IL-1 mRNA in murine cells by flow cytometry (FC) and fluorescent in situ hybridization (FISH)
AU Pennline, Kenneth J.; Pellerito-Bessette, Frances; Umland, Shelby P.; Siegel, Marvin I.; Smith, Sidney R.
CS Schering-Plough Res., Bloomfield, NJ, 07003, USA
SO Lymphokine Cytokine Res. (1992), 11(1), 65-71
CODEN: LCREEY; ISSN: 1056-5477
DT Journal
LA English
AB Flow cytometry (FC) and fluorescent in situ hybridization (FISH) were used to detect in vivo induced interleukin 1.alpha. (IL-1.alpha.) mRNA. Spleen cells and thioglycollate-induced peritoneal exudate cells (PEC) were harvested from Balb/c mice 3 h after i.p. injection of 20 .mu.g lipopolysaccharide (LPS). Cells from each population were phenotyped for MAC or I-Ad, fixed in 4% paraformaldehyde and then permeabilized with 70% ETOH. RNA-RNA FISH was performed by incubating suspended cells at 37.degree. for 17 h with biotinylated sense IL-1.alpha., antisense IL-1.alpha. or antisense IL-2 probes in 50% formamide. Hybridized cells were washed in 2X SSC, treated with ***RNAse*** , stained with avidin ***conjugated*** to fluorescein (FITC) or allophycocyanin (APC) and analyzed immediately by FC. Initially, avidin-FITC was used to detect hybridized probe. Dual fluorescent FC anal. of IL-1.alpha. mRNA expression in LPS stimulated I-Ad+ cells showed an increase in mean fluorescent intensity (MFI) of 51 log channels (0.25 logs) when compared to unstimulated cells. Addnl., induction of specific IL-1.alpha. mRNA expression in cells from LPS treated animals was illustrated by increases in percent pos. cells (24%) and in equiv. sol. fluorescein mols. (ESFM) bound (47%) when compared to cells from vehicle treated mice. Unhybridized cells and cells hybridized with control antisense IL-2 probe did not exhibit increases in MFI or ESFM. In subsequent expts. on MAC+ PEC, the use of avidin-APC to detect bound probe resulted in a greater sepn. between the FISH signals of antisense IL-1.alpha. and control sense probe than that seen with FITC. Thus, hybridization signals for a specific ***cytokine*** mRNA, induced in vivo, can be detected in defined, selected cell populations using dual fluorescent cytofluorometry.

L3 ANSWER 18 OF 18 CAPLUS COPYRIGHT 1999 ACS
AN 1991:183555 CAPLUS
DN 114:183555
TI Interleukin-6 mRNA and protein increase in vivo following induction of acute thrombocytopenia in mice
AU Cox, Louis H.; Downs, Tamyra; Dagg, Kathy; Henthorn, James; Burstein, Samuel A.
CS Health Sci. Cent., Univ. Oklahoma, Oklahoma City, OK, USA
SO Blood (1991), 77(2), 286-93
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
AB Induction of exptl. thrombocytopenia in rodents results in the enhancement of megakaryocytic growth and differentiation. Interleukin-3 (IL-3) and IL-6, ***cytokines*** with a broad spectrum of biol. activities, stimulate megakaryocytopoiesis in vitro. To det. if expression of these factors might increase in response to exptl. thrombocytopenia, steady-state levels of IL-3 and IL-6 mRNA was measured following rabbit antiplatelet serum (APS) injection. Groups of mice were injected i.v. with 0.2 mL APS while control animals received rabbit antilymphocyte serum (ALS), normal rabbit serum (NRS), or phosphate-buffered saline (PBS). At

various times up to 72 h after injection mice were exsanguinated and splenectomized. Platelet counts in the exptl. animals were less than 12% of controls. Splenic RNA was hybridized in soln. to 32P-UTP-labeled cRNA probes for IL-3 and IL-6. ***RNase*** -resistant ***hybrids*** were resolved on denaturing gels and visualized autoradiog. IL-3 ***hybrids*** were undetectable at all time points tested, irresp. of the film exposure time or specific activity of the probe. Conversely, IL-6 ***hybrids*** were easily visualized and showed peak expression at 1.5 to 2.0 h. By 3 h, IL-6 mRNA had returned almost to the level of the controls. Similar results were obsd. in the bone marrow, although maximal IL-6 mRNA in that tissue was obsd. 4 h following APS administration. To det. if this mRNA increment was assocd. with a concomitant increase in bioactive protein, serum was tested for its ability to stimulate IL-6-department B9 cells. At 1.75 h following injection, exptl. animals showed a small but significant increment in IL-6 activity compared with controls (200 U/mL IL-6 compared with 129 U/mL in ALS-injected controls, 106 U/mL in NRS-injected controls and 84 U/mL in PBS-injected controls). The data show that IL-6 mRNA and bioactive protein increase in responses to acute immunothrombocytopenia, while no increment in IL-3 is detectable. These results suggest that IL-6 may play a role in the physiol. response to acute immunothrombocytopenia.

=> s l3 1-18 kwic

MISSING OPERATOR L3 1-18
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> d l3 1-18 kwic

L3 ANSWER 1 OF 18 MEDLINE
AB . . . be preferable. In this study, the immunodominant B-cell epitope of sperm antigen Sp17 has been identified and synthesized as a ***chimeric*** peptide with the promiscuous T-cell epitope bovine ***RNase*** [94-104] at the N terminal. Immunization of female BALB/c mice with this peptide induced a dose-dependent reduction in fertility. Although antibodies. . . this apparent strain-specific infertility induction, a more extended study on both the humoral and the cellular immune response to the ***chimeric*** peptide was performed. The antigen-specific T-cell response and the levels of antigen-specific ***cytokines*** are the major factors that affect fertility outcome.

L3 ANSWER 2 OF 18 MEDLINE
AB . . . upstream of the translation start codon as the initiation site for transcription. This transcription start site has been confirmed by ***RNase*** protection analysis. Structural analysis of the 5' flanking region has revealed that the gene is TATA-less. This region, however, contains. . . recognition sites for SP1. There are also consensus sequences for the liver-specific transcription factor nuclear factor-1/L, for a variety of ***cytokine*** responsive factors, and for the xenobiotic responsive factor called the arylhydrocarbon receptor. Southern blot analysis of the genomic DNA from Chinese hamster-human and mouse-human ***hybrid*** cell lines and fluorescent in situ hybridization with human metaphase chromosome spreads have shown that the gene is located on. . .

L3 ANSWER 3 OF 18 MEDLINE
AB . . . cell-clot complexes and finally to sections from six paired nasal biopsies obtained before, during, or after HRV-proven colds. Specificity of ***hybrids*** was established by the absence of signal in uninfected tissue, in cells infected with other viruses, after ***RNase*** pretreatment, and with application of control probes. Hybridization signals were observed in epithelial cells in three of six biopsies obtained. . . cause productive infection of nasal epithelium during a cold and their intracellular localization may produce perturbation of inflammatory mediators and ***cytokine*** profiles.(ABSTRACT TRUNCATED AT 250 WORDS)

L3 ANSWER 4 OF 18 MEDLINE
AB Interleukin 4 (also known as "B cell stimulatory factor-1"), a ***cytokine*** product of T lymphocytes and mast cells, stimulates synthesis of the extracellular matrix proteins, types I and III collagen and. . . the levels of Pro alpha 1(I) collagen transcripts in IL-4-treated fibroblast cultures was also corroborated by antisense RNA-mRNA hybridization and ***RNAse*** resistant ***hybrids*** which showed that IL-4-treated fibroblasts expressed higher levels of Pro alpha 1(I) collagen transcripts. Nuclear run-off transcription experiments indicated that. . . level, resulting in synthesis of these extracellular matrix proteins. These and other data suggest that IL-4 may be a "fibrogenic ***cytokine*** " that could be important in promoting biogenesis of extracellular matrix proteins in normal wound healing and in pathological fibrosis in. . .

L3 ANSWER 5 OF 18 MEDLINE
AB Induction of experimental thrombocytopenia in rodents results in the enhancement of megakaryocytic growth and differentiation. Interleukin-3 (IL-3) and IL-6, ***cytokines*** with a broad spectrum of biologic activities, stimulate megakaryocytopoiesis in vitro. To determine if expression of these factors might increase. . . were less than 12% of controls. Splenic RNA was hybridized in solution to 32P-UTP-labeled cRNA probes for IL-3 and IL-6. ***RNase*** -resistant ***hybrids*** were resolved on denaturing gels and visualized autoradiographically. IL-3 ***hybrids*** were undetectable at all time points tested, irrespective of the film exposure time or specific activity of the probe. Conversely, IL-6 ***hybrids*** were easily visualized and showed peak expression at 1.5 to 2.0 hours. By 3 hours, IL-6 mRNA had returned almost. . .

L3 ANSWER 6 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB . . . have recently demonstrated that human and monkey are unique in having high plasma levels of C19 steroid glucuronides. These circulating ***conjugates*** have been proposed to reflect the peripheral conversion of adrenal and gonadal C19 steroids to potent androgens, esp. DHT. In. . . in breast and prostate tumor cell lines such as MCF-7 and LNCaP, resp. In agreement with the presence of steroid ***conjugating*** enzymes in extrahepatic tissues, UGT cDNA clones, which encode steroid ***conjugating*** proteins, have been isolated from libraries constructed from human and monkey prostate mRNA. The presence of UGT transcripts and proteins in extrahepatic tissues in both species, as detd. by Northern blot, ***RNase*** protection, specific RT-PCR, in situ hybridization, Western blot and immunocytochem. anal., indicate the relevance of steroid glucuronidation in tissues other. . . and UGT2B17, where only the expression of UGT2B17 was affected following treatments of LNCaP cells with androgens, growth factors or ***cytokines*** . Steroid ***conjugation*** by UGT enzymes is potentially involved in hormone inactivation in steroid target tissues, thus modifications in UGT expression levels may. . .

L3 ANSWER 7 OF 18 CAPLUS COPYRIGHT 1999 ACS
IT ***Cytokines***
RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(EDN (eosinophil-derived neurotoxin), ***fusion*** products with targeting antibody; selective cytotoxic reagents comprising ***RNase*** -active proteins fused to targeting antibodies)

L3 ANSWER 8 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB . . . be preferable. In this study, the immunodominant B-cell epitope of sperm antigen Sp17 has been identified and synthesized as a ***chimeric*** peptide with the promiscuous T-cell epitope bovine ***RNase*** [94-104] at the N terminal. Immunization of female BALB/c mice with this peptide induced a dose-dependent redn. in fertility. Although antibodies. . . this apparent strain-specific infertility induction, a more extended study on both the humoral and the cellular immune response to the ***chimeric*** peptide was performed. The antigen-specific T-cell response and the levels of antigen-specific ***cytokines*** are the major factors that affect fertility outcome.

L3 ANSWER 9 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB ***Cytokines*** are known to modulate the level of both phase 1 and phase 2 drug-metabolizing enzymes in hepatocytes. Although the effects of ***cytokines*** on cytochrome P 450(CYP450) enzymes are well understood, there is limited knowledge on how ***cytokines*** may affect steroid UDP-glucuronosyltransferase (UGT) phase 2 enzyme activity and expression in different cell types, including hepatocytes and steroid target. . . cells. LNCaP cells, which is a human prostate cancer cell line, is a good model to study the effect of ***cytokines*** in steroid target cells because it is known to express steroidogenic enzymes, including UGT2B15 and UGT2B17, which are widely expressed steroid UGT enzymes known to ***conjugate*** androgens. In this study, we examd. the possible interaction among interleukin-1.alpha. (IL-1.alpha.), IL-4, IL-6, and steroid UGT enzymes (UGT2B15 and. . . well as the DHT-induced proliferation of these cells. However, neither IL-4 nor IL-6 significantly affected the formation of DHT glucuronide. ***RNase*** protection and Western blot analyses demonstrated a specific redn. of UGT2B17 transcript and protein levels in IL-1.alpha.-treated LNCaP cells. The level of UGT2B15 was not affected by ***cytokine*** treatments, indicating a differential regulation between these two UGT enzymes. Transfection expts. performed with the UGT2B17 gene promoter region indicates. . . elements. This study indicates that cell proliferation and UGT expression in steroid-responsive cancer cells are differentially regulated depending on the ***cytokines*** present in the cell microenvironment.

L3 ANSWER 10 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB . . . upstream of the translation start codon as the initiation site for transcription. This transcription start site has been confirmed by ***RNase*** protection anal. Structural anal. of the 5' flanking region has revealed that the gene is TATA-less. This region, however, contains. . . recognition sites for SP1. There are also consensus sequences for the liver-specific transcription factor nuclear factor-1/L, for a variety of ***cytokine*** responsive factors, and for the xenobiotic responsive factor called the arylhydrocarbon receptor. Southern blot anal. of the genomic DNA from Chinese hamster-human and mouse-human ***hybrid*** cell lines and fluorescent in situ hybridization with human metaphase chromosome spreads have shown that the gene is located on. . .

L3 ANSWER 11 OF 18 CAPLUS COPYRIGHT 1999 ACS
IT ***Cytokines***
RL: BAC (Biological activity or effector, except adverse); BPN

(Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(EDN (eosinophil-derived neurotoxin), ***fusion*** products with onconase; expression and characterization of cytotoxic human-frog ***chimeric*** ***RNase*** and its potential for cancer therapy)

L3 ANSWER 12 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB . . . a different open reading frame (ORF) within the 37 N-terminal amino acids. The ORF when translated as a glutathione S-transferase ***fusion*** protein has B-cell growth factor activity. To study the expression pattern of this 12-kDa BCGF, DNA and RNA probes were. . . lymphocytes. Thus, mitogen-stimulated lymphocytes do not synthesize sufficient quantities of BCGF mRNA to be detected by Northern blot or by ***RNase*** protection analyses. This discrepancy with previous studies is probably explained by the unusual features of the sequence used in the. . . study, namely the presence of Alu sequences. Thus, 12-kDa BCGF should be excluded from the continuously growing list of cloned ***cytokines*** .

L3 ANSWER 13 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB . . . mechanisms of action: (1) a direct inhibition of one (or more) of the phases of the lentiviral biol. cycle (binding, ***fusion*** , RT and ***RNase*** activities), (2) a modulation of the immune capacities (ADCC and NK functions) that might result in an restoration of the. . . Indeed, three questions remain to be raised: (1) direct and/or indirect infection inhibition of macrophages, (2) the modulation of the ***cytokine*** network and (3) the efficiency of polyoxometalates in long-term treatment.

L3 ANSWER 14 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB . . . cell-clot complexes and finally to sections from 6 paired nasal biopsies obtained before, during, or after HRV-proven colds. Specificity of ***hybrids*** was established by the absence of signal in uninfected tissue, in cells infected tissue with other viruses, after ***RNase*** pretreatment, and with application of control probes. Hybridization signals were obsd. in epithelial cells in 3 of 6 biopsies obtained. . . cause productive infection of nasal epithelium during a cold and their intracellular localization may produce perturbation of inflammatory mediators and ***cytokine*** profiles. Use of ISH will permit studies exploring the pathogenesis of HRV-related symptoms and clarification of the mechanisms of lower. . .

L3 ANSWER 15 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB . . . contain multiple introns. The transcription start site and promoter region of the NOS3 gene were identified by primer extension and ***RNase*** protection assays. Sequencing of the putative promoter revealed consensus sequences for the shear stress-response element, as well as ***cytokine*** -responsive cis regulatory sequences, both possibly important to the roles played by NOS3 in the normal and the diseased cardiovascular system. The authors also mapped the chromosomal location of the NOS3 gene. First, a chromosomal panel of human-rodent somatic cell ***hybrids*** was screened using PCR with oligonucleotide primers derived from the NOS3 genomic clone. The specificity of the amplified PCR product. . .

L3 ANSWER 16 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB Interleukin 4 (also known as B cell stimulatory factor-1), a ***cytokine*** product of T lymphocytes and mast cells, stimulates synthesis of the extracellular matrix proteins, types I and III collagen, and. . . of the levels of Pro .alpha.1(I) collagen transcripts in IL-4-treated fibroblast cultures was also corroborated by antisense RNA-mRNA hybridization and ***RNAse*** resistant ***hybrids*** which showed that IL-4-treated fibroblasts expressed higher levels of Pro .alpha.1(I) collagen transcripts. Nuclear run-off transcription expts. indicated that IL-4. . . level, resulting in synthesis of these extracellular matrix proteins. These and other data suggest that IL-4 may be a fibrogenic ***cytokine*** that could be important in promoting biogenesis of extracellular matrix proteins in normal wound healing and in pathol. fibrosis in. . .

L3 ANSWER 17 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB . . . sense IL-1.alpha., antisense IL-1.alpha. or antisense IL-2 probes in 50% formamide. Hybridized cells were washed in 2X SSC, treated with ***RNAse*** , stained with avidin ***conjugated*** to fluorescein (FITC) or allophycocyanin (APC) and analyzed immediately by FC. Initially, avidin-FITC was used to detect hybridized probe. Dual. . . FISH signals of antisense IL-1.alpha. and control sense probe than that seen with FITC. Thus, hybridization signals for a specific ***cytokine*** mRNA, induced in vivo, can be detected in defined, selected cell populations using dual fluorescent cytofluorometry.

L3 ANSWER 18 OF 18 CAPLUS COPYRIGHT 1999 ACS
AB Induction of exptl. thrombocytopenia in rodents results in the enhancement of megakaryocytic growth and differentiation. Interleukin-3 (IL-3) and IL-6, ***cytokines*** with a broad spectrum of biol. activities, stimulate megakaryocytopoiesis in vitro. To det. if expression of these factors might increase. . . were less than 12% of controls. Splenic RNA was hybridized in soln. to 32P-UTP-labeled cRNA probes for IL-3 and IL-6. ***RNase*** -resistant ***hybrids*** were resolved on denaturing gels and visualized autoradiog. IL-3 ***hybrids*** were undetectable at all time points tested, irresp. of the film exposure time or specific activity of the probe. Conversely, IL-6 ***hybrids*** were easily visualized and showed peak expression at 1.5 to 2.0 h. By 3 h, IL-6 mRNA had returned almost. . .